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Ambient Water Quality Criteria for Hexachlorocyclohexane

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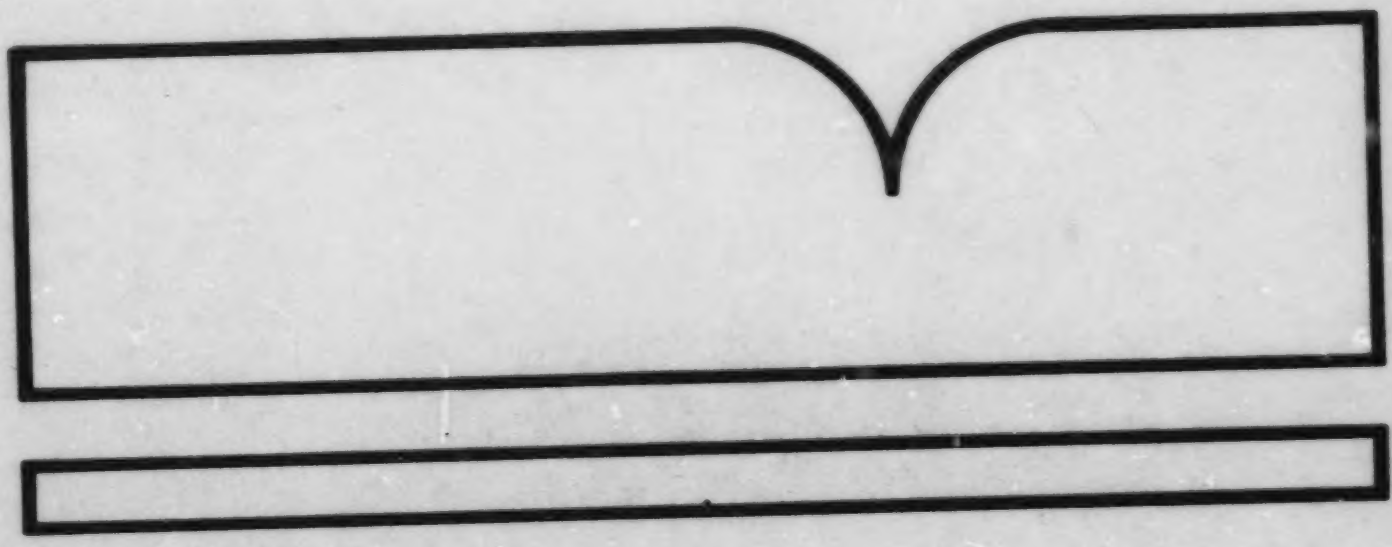

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Ambient Water Quality Criteria for Hexachlorocyclohexane

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16. ABSTRACT

Section 304(A) of the Clean Water Act [33 U.S.C. 1314(A)], requires EPA to publish and periodically update water quality criteria. These criteria are to reflect the latest scientific knowledge on the identifiable effects of pollutants on public health and welfare, aquatic life, and recreation. This report presents water quality criteria for Hexachlorocyclohexane. It presents concentration criteria for the protection of freshwater and saltwater aquatic life. It presents 'safe' concentrations for humans, and in the case of suspect or proven carcinogens, gives various levels of incremental cancer risk. A Section 304(A) water quality criterion is a qualitative or quantitative estimate of the concentration of a water constituent or pollutant in ambient waters which, when not exceeded, will ensure a water quality sufficient to protect a specified water use. Under the Act a criterion is a scientific entity, based solely on data and scientific judgment. It does not reflect considerations of economic or technological feasibility nor is it a water quality standard and in itself has no regulatory effect.

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AMBIENT WATER QUALITY CRITERIA FOR

HEXACHLOROCYCLOHEXANE

Prepared By
U.S. ENVIRONMENTAL PROTECTION AGENCY

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FOREWORD

Section 304 (a)(1) of the Clean Water Act of 1977 (P.L. 95-217), requires the Administrator of the Environmental Protection Agency to publish criteria for water quality accurately reflecting the latest scientific knowledge on the kind and extent of all identifiable effects on health and welfare which may be expected from the presence of pollutants in any body of water, including ground water. Proposed water quality criteria for the 65 toxic pollutants listed under section 307 (a)(1) of the Clean Water Act were developed and a notice of their availability was published for public comment on March 15, 1979 (44 FR 15926), July 25, 1979 (44 FR 43660), and October 1, 1979 (44 FR 56628). This document is a revision of those proposed criteria based upon a consideration of comments received from other Federal Agencies, State agencies, special interest groups, and individual scientists. The criteria contained in this document replace any previously published EPA criteria for the 65 pollutants. This criterion document is also published in satisifaction of paragraph 11 of the Settlement Agreement in Natural Resources Defense Council, et. al. vs. Train, 8 ERC 2120 (D.D.C. 1976), modified, 12 ERC 1833 (D.D.C. 1979).

The term "water quality criteria" is used in two sections of the Clean Water Act, section 304 (a)(1) and section 303 (c)(2). The term has a different program impact in each section. In section 304, the term represents a non-regulatory, scientific assessment of ecological effects. The criteria presented in this publication are such scientific assessments. Such water quality criteria associated with specific stream uses when adopted as State water quality standards under section 303 become enforceable maximum acceptable levels of a pollutant in ambient waters. The water quality criteria adopted in the State water quality standards could have the same numerical limits as the criteria developed under section 304. However, in many situations States may want to adjust water quality criteria developed under section 304 to reflect local environmental conditions and human exposure patterns before incorporation into water quality standards. It is not until their adoption as part of the State water quality standards that the criteria become regulatory.

Guidelines to assist the States in the modification of criteria presented in this document, in the development of water quality standards, and in other water-related programs of this Agency, are being developed by EPA.

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TABLE OF CONTENTS

	Page
Criteria Summary	
Introduction	A-1
Aquatic Life Toxicology	B-1
Introduction	B-1
Effects	B-2
Acute Toxicity	B-2
Chronic Toxicity	B-4
Plant Effects	B-5
Residues	B-6
Miscellaneous	B-8
Summary	B-8
Criteria	B-9
References	B-27
Mammalian Toxicology and Human Health Effects	C-1
Introduction	C-1
Exposure	C-4
Ingestion from Water	C-4
Ingestion from Food	C-5
Inhalation	C-7
Dermal	C-7
Pharmacokinetics	C-8
Absorption	C-8
Distribution	C-9
Metabolism	C-10
Excretion	C-12
Effects	C-16
Acute, Subacute, and Chronic Toxicity	C-16
Synergism and/or Antagonism	C-23
Teratogenicity	C-25
Mutagenicity	C-27
Carcinogenicity	C-27
Criterion Formulation	C-34
Existing Guidelines and Standards	C-34
Current Levels of Exposure	C-34
Special Groups at Risk	C-35
Basis and Derivation of Criteria	C-36
References	C-41
Appendix	C-57

CRITERIA DOCUMENT

HEXACHLOROCYCLOHEXANE

CRITERIA

Aquatic Life

Lindane

For lindane the criterion to protect freshwater aquatic life as derived using the Guidelines is 0.080 µg/l as a 24-hour average and the concentration should not exceed 2.0 µg/l at any time.

For saltwater aquatic life the concentration of lindane should not exceed 0.16 µg/l at any time. No data are available concerning the chronic toxicity of lindane to sensitive saltwater aquatic life.

BHC

The available data for a mixture of isomers of BHC indicate that acute toxicity to freshwater aquatic life occurs at concentrations as low as 100 µg/l and would occur at lower concentrations among species that are more sensitive than those tested. No data are available concerning the chronic toxicity of a mixture of isomers of BHC to sensitive freshwater aquatic life.

The available data for a mixture of isomers of BHC indicate that acute toxicity to saltwater aquatic life occurs at concentrations as low as 0.34 µg/l and would occur at lower concentrations among species that are more sensitive than those tested. No data are available concerning the chronic toxicity of a mixture of isomers of BHC to sensitive saltwater aquatic life.

Human Health

For the maximum protection of human health from the potential carcinogenic effects due to exposure of α-hexachlorocyclohexane through ingestion of contaminated water and contaminated aquatic organisms, the ambient water

concentrations should be zero based on the non-threshold assumption for this chemical. However, zero level may not be attainable at the present time. Therefore, the levels which may result in incremental increase of cancer risk over the lifetime are estimated at 10^{-5}, 10^{-6}, and 10^{-7}. The corresponding recommended criteria are 92 ng/l, 9.2 ng/l, and 0.92 ng/l, respectively. If the above estimates are made for consumption of aquatic organisms only, excluding consumption of water, the levels are 310 ng/l, 31.0 ng/l, and 3.10 ng/l, respectively.

For the maximum protection of human health from the potential carcinogenic effects due to exposure of β-hexachlorocyclohexane through ingestion of contaminated water and contaminated aquatic organisms, the ambient water concentrations should be zero based on the non-threshold assumption for this chemical. However, zero level may not be attainable at the present time. Therefore, the levels which may result in incremental increase of cancer risk over the lifetime are estimated at 10^{-5}, 10^{-6}, and 10^{-7}. The corresponding recommended criteria are 163 ng/l, 16.3 ng/l, and 1.63 ng/l, respectively. If the above estimates are made for consumption of aquatic organisms only, excluding consumption of water, the levels are 547 ng/l, 54.7 ng/l, and 5.47 ng/l, respectively.

For the maximum protection of human health from the potential carcinogenic effects due to exposure of γ-hexachlorocyclohexane through ingestion of contaminated water and contaminated aquatic organisms, the ambient water concentrations should be zero based on the non-threshold assumption for this chemical. However, zero level may not be attainable at the present time. Therefore, the levels which may result in incremental increase of cancer risk over the lifetime are estimated at 10^{-5}, 10^{-6}, and 10^{-7}. The corresponding recommended criteria are 186 ng/l, 18.6 ng/l, and 1.86 ng/l,

respectively. If the above estimates are made for consumption of aquatic organisms only, excluding consumption of water, the levels are 625 ng/l, 62.5 ng/l, and 6.25 ng/l, respectively.

For the maximum protection of human health from the potential carcinogenic effects due to exposure of technical-hexachlorocyclohexane through ingestion of contaminated water and contaminated aquatic organisms, the ambient water concentrations should be zero based on the non-threshold assumption for this chemical. However, zero level may not be attainable at the present time. Therefore, the levels which may result in incremental increase of cancer risk over the lifetime are estimated at 10^{-5}, 10^{-6}, and 10^{-7}. The corresponding recommended criteria are 123 ng/l, 12.3 ng/l, and 1.23 ng/l, respectively. If the above estimates are made for consumption of aquatic organisms only, excluding consumption of water, the levels are 414 ng/l, 41.4 ng/l, and 4.14 ng/l, respectively.

Using the present guidelines, satisfactory criteria cannot be derived at this time due to the insufficiency in the available data for δ- and ε-hexachlorocyclohexane.

INTRODUCTION

Hexachlorocyclohexane is a broad spectrum insecticide of the group of cyclic chlorinated hydrocarbons called organochlorine insecticides. It consists of a mixture of five configurational isomers and was introduced in 1942 as a contact insecticide under the trade names BHC, benzene hexachloride, and 666. Since its introduction, both the used and production volume of technical grade BHC have undergone dramatic changes as a result of the discovery that virtually all of the insecticidal activity of BHC resides with its γ-isomer. By voluntary action, the principal domestic producer of technical grade BHC requested cancellations of its BHC registrations on September 1, 1976. As of July 21, 1978 all registrants of pesticide products containing BHC voluntarily cancelled their registrations or switched their former BHC products to lindane formulations. On the other hand, significant commercial use of the purified γ-isomer of BHC (lindane) continues. As of January 17, 1977, there were 557 Federal registrations for pesticide products containing lindane and 87 formerly State-registered products containing lindane for which Federal registration has been requested.

Hexachlorocyclohexane, commonly referred to as BHC or benzene hexachloride, is a brownish-to-white crystalline solid with a phosgene-like odor, a molecular formula of $C_6H_6Cl_6$, a molecular weight of 290.0, a melting point of 65°C, and a solubility in water of 10 to 32 mg/l (Hardie, 1972; Clristensen, 1976; Matsumura, 1975). BHC is the common name approved by the International Standards Organization for the mixed configurational isomers of 1,2,3,4,5,6-hexachlorocyclohexane, although the terms BHC and benzene hexachloride are misnomers for this aliphatic compound and should not be confused with aromatic compounds of similar structure, such as the aromatic

compound hexachlorobenzene (Int. Agency Res. Cancer, 1974). Lindane is the common name approved by the International Standards Organization for the γ-isomer of 1,2,3,4,5,6-hexachlorocyclohexane. BHC is synthesized by the direct action of chlorine on benzene in the presence of ultraviolet light (Hardie, 1972).

Technical grade BHC contains the hexachlorocyclohexane isomers in the following ranges: α-isomer, 55 to 70 percent; β-isomer, 6 to 8 percent; γ-isomer, 10 to 18 percent; δ-isomer, 3 to 4 percent; ε-isomer, trace amounts (Hardie, 1972). The actual content of the isomers in technical grade BHC varies depending on the manufacturing conditions.

In addition to the hexachlorocyclohexane isomers, technical grade BHC may contain varying quantities (three to five percent) of other chlorinated derivatives of cyclohexane primarily heptachlorocyclohexane and octachlorocyclohexane.

Technical grade BHC is available in various formulations as wettable powders, granules, dusts, and emulsifiable concentrates and can be used as a stomach and contact poison for a wide variety of insect pests and animal parasites. Since the γ-isomer (lindane) has been shown to be the insecticidally active ingredient in technical grade BHC (Hardie, 1972), technical grade BHC now has limited use commercially except as the raw material from which the purified γ-isomer is extracted by a process of selective crystallization.

Technical grade lindane is composed of 99 to 100 percent pure γ-BHC isomer and is available in the form of emulsifiable concentrates, wettable powders, dusts, crystals, and solids for smoke generators and thermal vaporizers.

The physical properties of the purified BHC isomers are presented in Table 1.

TABLE 1

Physical Properties of BHC Isomers*

BHC Isomer	Melting Point (°C)	Vapor Pressure (mm Hg at 50°C)	Water Solubility (mg/l)	Solubility in Relatively Non-polar Solvent (g/100 g ether at 20°C)
alpha	158	0.00087	10	6.2
beta	312	0.000014	5	1.8
gamma	112.5	0.0008	10	20.8
delta	138	---	10	35.4

*Source: Hardie, 1972; Ulmann, 1972

The isomers of BHC are not susceptible to photolysis or strong acids but are, with the exception of the β-isomer, dehydrochlorinated by alkalies to form primarily 1,2,4-trichlorobenzene (Hardie, 1972). Lindane has been shown to be slowly degraded (ten percent degradation after six weeks) by soil microorganisms (Mathur and Saha, 1975) and is capable of isomerization to α- and/or δ-BHC by microorganisms and plants (Matsumura, et al. 1976; Newland, et al. 1969; Steinwandeter, 1976).

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Aquatic Life Toxicology*

INTRODUCTION

Hexachlorocyclohexane is a member of the group of cyclic chlorinated hydrocarbons called organochlorine insecticides. It is manufactured by the chlorination of benzene and is commonly called BHC or benzene hexachloride. Hexachlorocyclohexane is an aliphatic compound, and it should not be confused with aromatic compounds of a similar structure. The aromatic compounds are also called BHC, benzene hexachloride or hexachlorobenzene, so caution is advised when reading reports on these chemicals.

Hexachlorocyclohexane primarily consists of five configurational isomers, sold under the trade name BHC (benzene hexachloride) and Compound-666. Technical grade BHC contains five hexachlorocyclohexane isomers in the following ranges: alpha isomer, 55 to 70 percent; beta isomer, 6 to 8 percent; gamma isomer, 10 to 18 percent; delta isomer, 3 to 4 percent; and epsilon isomer, trace amounts. The gamma isomer (lindane, a pesticide) is the isomer with insecticidal properties and is usually considered to be the isomer most toxic to aquatic organisms. Preparations which contain at least 99 percent of the gamma isomer are called lindane, and lindane is the most important hexachlorocyclohexane isomer.

The majority of the freshwater and saltwater effects data are for the gamma isomer, lindane, and criteria were developed for this compound. There are additional data for technical BHC, which contains varying amounts of the

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*The reader is referred to the Guidelines for Deriving Water Quality Criteria for the Protection of Aquatic Life and Its Uses in order to better understand the following discussion and recommendation. The following tables contain the appropriate data that were found in the literature, and at the bottom of each table are calculations for deriving various measures of toxicity as described in the Guidelines.

gamma and alpha isomers. The data for these compounds are included in the tables but are insufficient for criteria development.

EFFECTS

Acute Toxicity

Of the 33 freshwater acute toxicity test results reported in Table 1, all are with lindane; seven invertebrate and 15 fish species were tested. Most tests were 96-hour static tests based on unmeasured concentrations; only three were tests with measured concentrations, of which only one used flow-though procedures.

Nine toxicity tests with lindane and seven freshwater invertebrate species are reported in Table 1. The data can be separated into three toxicological groups. The three cladoceran species are the most resistant organisms tested. Their species mean acute values range from 460 to 676 ug/l, or about 10 to 70 times higher than the LC_{50} concentrations for the most sensitive group. The crustaceans, represented by the sowbugs and scud, are generally the most sensitive species tested; their LC_{50} values range from 10 to 48 ug/l. The middle group, represented by an insect, a chironomid, had an LC_{50} of 207 ug/l, which is between the concentrations toxic to the cladoceran and crustacean species.

Acute values for lindane with 15 freshwater fish species (Table 1) range from 2 to 141 ug/l for brown trout and goldfish, respectively. These values represent differences among species in their responses to lindane exposure. Generally, the warmwater fish species appear to be more tolerant of lindane than do the coldwater salmonid species; this is also shown by the additional fish acute data in Table 6. Frog and toad species were even more resistant than warmwater fish species (Table 6).

The 96-hour LC_{50} values for BHC (Table 6) are much higher than those for lindane. The difference cannot be explained by simple ratio of the lindane content in the BHC to pure lindane. For example, Henderson, et al. (1959) based their LC_{50} values for BHC on the gamma isomer content and found that the gamma isomer in BHC was approximately 244 times less toxic to the fathead minnow in soft water than the gamma isomer tested alone. In fact, the BHC concentrations were so high that precipitates were observed. In addition, they determined that a concentration of 100 ug/l of lindane alone cause 100 percent mortality of fathead minnows in 24 hours. When 3,200 ug/l of technical BHC, a concentration that caused no mortality, and 100 ug/l lindane were added to the same tank, no mortality occurred within 96 hours. They concluded that the other BHC isomers either reduced the solubility of the gamma isomer (lindane) or had an antagonistic effect, reducing its toxicity.

The Freshwater Final Acute Value for lindane, derived from the species mean acute values listed in Table 3 using the procedure described in the Guidelines, is 2.2 ug/l. However, the brown trout has a species mean acute value of 2 ug/l (Table 3). Therefore, the Freshwater Final Acute Value for lindane should be lowered to 2.0 ug/l to protect this important species. Insufficient data are available for BHC to derive a Freshwater Final Acute Value according to the Guidelines.

Acute toxicity values for BHC and lindane with saltwater invertebrate species range from 0.17 to 3,680 ug/l (Table 1). Saltwater invertebrate species are generally more sensitive than fish species to lindane. The LC_{50} for the commercially important pink shrimp, Penaeus duorarum, is more than one order of magnitude lower than the second most sensitive species. The least sensitive invertebrate species was the polychaete, Neanthes aren-

aceodentata, with a 96-hour LC_{50} value of 3,680 ug/l, 21,000 times greater than that of the pink shrimp. A single LC_{50} value was available for a saltwater invertebrate species and BHC. The 96-hour LC_{50} for pink shrimp based on measured concentrations was 0.34 ug/l, indicating BHC to be less toxic than lindane (Schimmel, et al. 1977).

Although saltwater fish species have a wide range of sensitivity to lindane (Table 1), they are generally less sensitive than saltwater invertebrate species. Eleven species of fishes were tested in static and flow-through exposures. Only two species were exposed for 96 hours under flow-through conditions with measured concentrations. These LC_{50} values were 30.6 ug/l for the pinfish and 103.9 ug/l for the sheepshead minnow (Schimmel, et al. 1977). LC_{50} values, acceptable according to the Guidelines and including nine other species, have a range from 7.3 to 103.9 ug/l (Table 1). Only one test was conducted on a saltwater fish species using BHC. The 96-hour LC_{50} from a flow-through test with measured concentrations was 86.4 ug/l for pinfish (Schimmel, et al. 1977). This compares to a 30.6 ug/l LC_{50} for the same species under the same conditions for lindane, indicating a lesser toxicity for BHC (Schimmel, et al. 1977).

The Saltwater Final Acute Value for lindane, derived from the species mean acute values listed in Table 3 using the procedure described in the Guidelines, is 0.16 ug/l. Insufficient data were found on acute toxicity of BHC to saltwater species to derive a Saltwater Final Acute Value for BHC.

Chronic Toxicity

Chronic data are available for three freshwater invertebrate species (Table 2). Chronic values for Daphnia magna, Gammarus fasciatus, and Chironomus tentans are 14.5, 6.1, and 3.3 ug/l, respectively. Acute-chronic ratios are calculable for two invertebrate species; these values are 33 for

Daphnia magna and 63 for Chironomus tentanus. An acute-chronic ratio was not calculated for Gammarus fasciatus because no appropriate acute value was available.

Only one acceptable chronic test with a fish species was found (Macek, et al. 1976). A chronic value of 14.6 ug/l was calculated for the fathead minnow (Table 2). No 96-hour LC_{50} values were obtained with fathead minnows in water of the same quality, even though duplicate flow-through acute toxicity tests were conducted, and lindane concentrations were measured. In both cases the LC_{50} was >100 ug/l but was not calculated. After 11 days incipient LC_{50} values of 62.5 and 75.6 ug/l were determined. The geometric mean of the three acute values for fathead minnows in Table 1 is 67.1 ug/l which is close to the mean of the 11-day values. Thus, 110 ug/l can probably be used as a reasonable estimate of the flow-through LC_{50} for fathead minnows. This results in an acute-chronic ratio of 7.5 for fathead minnows (Table 2) and a Freshwater Final Chronic Value of 0.080 ug/l (Table 3).

No chronic toxicity values for hexachlorocyclohexane were found for any saltwater invertebrate or fish species.

Plant Effects

The effect of hexachlorocyclohexane on freshwater plants (Table 4) must be estimated from only one report (Krishnakumari, 1977). Growth inhibition of an alga, Scenedesmus acutus, was reported at 500 to 5,000 ug/l, depending on the isomer used in the exposures. The alpha isomer was the most toxic at 500 ug/l, whereas the more commonly used gamma isomer (lindane) inhibited growth at 1,000 ug/l. The gamma isomer effect concentration is about 10,000 times higher than the freshwater chronic value, so the plants should be protected.

Hexachlorocyclohexane affected saltwater plants at concentrations greater than concentrations affecting animals (Table 4). A 28.5 percent decrease in productivity of natural phytoplankton communities occurred at a concentration of 1,000 ug/l lindane (Butler, 1963). Exposure to concentrations of alpha-hexachlorocyclohexane up to the solubility limit for the culture medium (1,400 ug/l) showed no toxicity to the marine algae, Chlamydomonas sp. or Dunaliella sp. (Canton, et al. 1977, 1978).

Residues

Freshwater bioconcentration factors (BCF) (Table 5) include mean factors determined using data obtained from a small oligotrophic lentic ecosystem (a flooded limestone quarry), where the fate of introduced lindane and DDE was followed for one year by Hamelink and Waybrant (1976). They reported average steady-state bioconcentration factors for lindane of 768 and 486 for whole bluegills and rainbow trout, respectively. They used mean concentration data from all thermal strata under summer water conditions to calculate their bluegill concentration factor. This value (768) was not used because the bluegill would probably stay above the thermocline. Seventy percent of the lindane was evenly distributed in the epilimnion, and concentrations were relatively constant until fall turnover (destratification). After turnover, the lindane concentrations were similar throughout the water column. Their rainbow trout BCF data were obtained under these conditions.

The remaining available BCF values (Table 5) are those of Macek, et al. (1976) obtained under laboratory conditions. These BCF values are for muscle tissue in bluegill (35) and brook trout (70) and for eviscerated fathead minnows (477).

The bioconcentration of hexachlorocyclohexane from water into the tissues of saltwater organisms has been relatively well studied (Table 5). Steady-state BCF values are available for American oysters and pinfish (Schimmel, et al. 1977). Compared to many of the chlorinated insecticides, the BCF values at steady-state are low. American oysters exposed continuously for 28 days to BHC bioconcentrated an average of 218 times the amount measured in the exposure water. Only in the highest exposure concentration, 0.093 µg/l, did the insecticide accumulate sufficiently high for accurate measurement. Pinfish exposed to BHC for 28 days bioconcentrated in edible tissue an average of 130 times the amount in water. The average BCF in offal (head and viscera) was 617. The relative percentages of the four isomers in BHC were similar to those in pinfish offal and edible tissues. Apparently, no individual isomer was stored or purged selectively. Oysters and pinfish depurated all detectable BHC within one week after being placed in BHC-free water.

Additional data on the bioconcentration of lindane and BHC are available for other organisms, but it is doubtful that the concentrations in the organisms are at steady-state (Table 6). The average bioconcentration factors after four days of exposure to lindane were 63 for grass shrimp, 84 for pink shrimp, 490 for sheepshead minnow, and 218 for pinfish (Schimmel, et al. 1977). In the same study, the average bioconcentration factors after four days of exposure to BHC were 80 for pink shrimp and 482 for pinfish. The four isomers of BHC were bioconcentrated in tissues of pink shrimp and pinfish in approximately the same relative amounts as in the insecticide formulation. Saltwater phytoplanktons rapidly accumulate and depurate BHC (Canton, et al. 1977).

No Freshwater of Saltwater Final Residue Value can be calculated because the only maximum permissible tissue concentration is a U.S. Food and Drug Administration (FDA) action level for frog legs.

Miscellaneous

None of the additional data included in Table 6 but not yet discussed would alter the freshwater criteria for lindane or contribute significantly to the derivation of a criterion for BHC or a saltwater criterion for lindane.

Summary

Data are available estimating the acute toxicity of lindane to seven freshwater invertebrate and 15 fish species. Freshwater crustaceans (sowbug and scud) are the most sensitive invertebrate species tested, and cladocerans are the most resistant. The range of species mean acute values for invertebrate species is 10 to 676 µg/l. Among the fish species tested, brown trout is the most sensitive with an acute value of 2 µg/l; goldfish is least sensitive with a value of 141 µg/l. The Freshwater Final Acute Value for lindane is 2.0 µg/l. No acute data are available for other hexachlorocyclohexane isomers and freshwater animals.

Acute toxicity data for lindane are available for eight saltwater invertebrate and 11 fish species. Acute values for invertebrate species range from 0.17 to 3,680 µg/l. Pink shrimp are the most sensitive species tested, and the polychaete, Neanthes arenaceodentata, is the least sensitive. Saltwater fish species tested have a wide range of sensitivity to lindane and are generally less sensitive than the invertebrate species; LC_{50} values range from 7.3 to 104 µg/l. The Saltwater Final Acute Value for lindane is 0.16 µg/l. Data are available for BHC with one saltwater invertebrate and one fish species and indicate that BHC is less toxic than lindane.

Chronic values for lindane are available for three freshwater invertebrate species and range from 3.3 µg/l for the midge, Chironomus tentans, to 14.5 µg/l for Daphnia magna. A chronic value of 14.6 µg/l is available for the fathead minnow. Acute-chronic ratios range from 7.5 for fathead minnow to 63 for the midge, and the Freshwater Final Chronic Value for lindane is 0.080 µg/l. No chronic data are available for any other hexachlorocyclohexane isomers nor for any saltwater species.

Acute tests with a freshwater alga and three different BHC isomers indicated that the alpha isomer is more toxic than are gamma (lindane) and beta. Both freshwater and saltwater algal species were much more resistant to hexachlorocyclohexane than were the invertebrate and fish species tested.

Bioconcentration factors for lindane with a variety of freshwater fish species ranged from 35 to 486; bioconcentration factors for saltwater species ranged from 130 to 617. No useful FDA action level or result of a chronic feeding study with wildlife is available for calculation of a Final Residue Value.

CRITERIA

Lindane

For lindane the criterion to protect freshwater aquatic life as derived using the Guidelines is 0.080 µg/l as a 24-hour average, and the concentration should not exceed 2.0 µg/l at any time.

For saltwater aquatic life the concentration of lindane should not exceed 0.16 µg/l at any time. No data are available concerning the chronic toxicity of lindane to sensitive saltwater aquatic life.

BHC

The available data for a mixture of isomers of BHC indicate that acute toxicity to freshwater aquatic life occurs at concentrations as low as 100

µg/l and would occur at lower concentrations among any species that are more sensitive than those tested. No data are available concerning the chronic toxicity of a mixture of isomers of BHC to sensitive freshwater aquatic life.

The available data for a mixture of isomers of BHC indicate that acute toxicity to saltwater aquatic life occurs at concentrations as low as 0.34 µg/l and would occur at lower concentrations among any species that are more sensitive than those tested. No data are available concerning the chronic toxicity of a mixture of isomers of BHC to sensitive saltwater aquatic life.

Table 1. Acute values for hexachlorocyclohexane

Species	Method[a]	Chemical	LC50/EC50 (µg/l)	Species Mean Acute Value (µg/l)	Reference
		FRESHWATER SPECIES			
		Lindane			
Cladoceran, *Daphnia pulex*	S, U	Lindane	460	460	Sanders & Cope, 1966
Cladoceran, *Daphnia magna*	S, M	Lindane	485	485	Macek, et al. 1976
Cladoceran, *Simocephalus serrulatus*	S, U	Lindane	520	-	Sanders & Cope, 1966
Cladoceran, *Simocephalus serrulatus*	S, U	Lindane	880	676	Sanders & Cope, 1966
Sowbug, *Asellus brevicaudus*	S, U	Lindane (99%)	10	10	Sanders, 1972
Scud, *Gammarus lacustris*	S, U	Lindane	48	48	Sanders, 1969
Scud, *Gammarus fasciatus*	S, U	Lindane (99%)	10	-	Sanders, 1972
Scud, *Gammarus fasciatus*	S, U	Lindane (99%)	11	10.5	Sanders, 1972
Midge, *Chironomus tentans*	S, M	Lindane	207	207	Macek, et al. 1976
Rainbow trout, *Salmo gairdneri*	S, U	Lindane	27	-	Macek & McAllister, 1970
Rainbow trout, *Salmo gairdneri*	S, U	Lindane (98%)	38	32	Katz, 1961
Brown trout, *Salmo trutta*	S, U	Lindane	2	2	Macek & McAllister, 1970
Brook trout, *Salvelinus fontinalis*	FT, M	Lindane	44.3	44.3	Macek, et al. 1976

Table 1. (Continued)

Species	Method*	Chemical	LC50/EC50 (µg/l)	Species Mean Acute Value (µg/l)	Reference
Coho salmon, *Oncorhynchus kisutch*	S, U	Lindane	41	-	Macek & McAllister, 1970
Coho salmon, *Oncorhynchus kisutch*	S, U	Lindane (100%)	50	45.3	Katz, 1961
Chinook salmon, *Oncorhynchus tshawytscha*	S, U	Lindane (100%)	40	40	Katz, 1961
Goldfish, *Carassius auratus*	S, U	Lindane	131	-	Macek & McAllister, 1970
Goldfish, *Carassius auratus*	S, U	Lindane (100%)	152	141.1	Henderson, et al. 1959
Carp, *Cyprinus carpio*	S, U	Lindane	90	90	Macek & McAllister, 1970
Fathead minnow, *Pimephales promelas*	S, U	Lindane	87	-	Macek & McAllister, 1970
Fathead minnow, *Pimephales promelas*	S, U	Lindane (100%)	62	-	Henderson, et al. 1959
Fathead minnow, *Pimephales promelas*	S, U	Lindane (100%)	56	67.1	Henderson, et al. 1959
Black bullhead, *Ictalurus melas*	S, U	Lindane	64	64	Macek & McAllister, 1970
Channel catfish, *Ictalurus punctatus*	S, U	Lindane	44	44	Macek & McAllister, 1970
Guppy, *Poecilia reticulata*	S, U	Lindane (100%)	138	138	Henderson, et al. 1959
Bluegill, *Lepomis macrochirus*	S, U	Technical lindane	54	-	Macek, et al. 1969
Bluegill, *Lepomis macrochirus*	S, U	Technical lindane	51	-	Macek, et al. 1969

Table 1. (Continued)

Species	Method*	Chemical	LC50/EC50 (µg/l)	Species Mean Acute Value (µg/l)	Reference
Bluegill, Lepomis macrochirus	S, U	Technical lindane	37	-	Macek, et al. 1969
Bluegill, Lepomis macrochirus	S, U	Lindane	68	-	Macek & McAllister, 1970
Bluegill, Lepomis macrochirus	S, U	Lindane (100%)	77	55.6	Henderson, et al. 1959
Redear sunfish, Lepomis microlophus	S, U	Lindane	83	83	Macek & McAllister, 1970
Largemouth bass, Micropterus salmoides	S, U	Lindane	32	32	Macek & McAllister, 1970
Yellow perch, Perca flavescens	S, U	Lindane	68	68	Macek & McAllister, 1970
		SALTWATER SPECIES			
		Lindane			
American oyster, Crassostrea virginica	FT, U	Technical lindane	450**	450	Butler, 1963
Mysid, Mysidopsis bahia	FT, M	Technical lindane	6.28	6.28	Schimmel, et al. 1977
Sand shrimp, Crangon septemspinosa	S, U	Lindane***	5.0	5.0	Eisler, 1969
Hermit crab, Pagurus longicarpus	S, U	Lindane***	5.0	5.0	Eisler, 1969
Grass shrimp, Palaemonetes pugio	FT, M	Technical lindane	4.44	4.44	Schimmel, et al. 1977
Grass shrimp, Palaemonetes vulgaris	S, U	Lindane***	10.0	10.0	Eisler, 1969
Pink shrimp, Penaeus duorarum	FT, M	Technical lindane	0.17	0.17	Schimmel, et al. 1977

Table 1. (Continued)

Species	Method[a]	Chemical	LC50/EC50 (µg/l)	Species Mean Acute Value (µg/l)	Reference
Polychaete, *Neanthes arenaceodentata*	S, M	Technical lindane	3,680	3,680	U.S. EPA, 1980
American eel, *Anguilla rostrata*	S, U	Technical lindane	56.0	56.0	Eisler, 1970
Sheepshead minnow, *Cyprinodon variegatus*	FT, M	Lindane***	103.9	103.9	Schimmel, et al. 1977
Mummichog, *Fundulus heteroclitus*	S, U	Technical lindane	60.0	60.0	Eisler, 1970
Striped killifish, *Fundulus majalis*	S, U	Technical lindane	28.0	28.0	Eisler, 1970
Atlantic silverside, *Menidia menidia*	S, U	Technical lindane	9.0	9.0	Eisler, 1970
Threespine stickleback, *Gasterosteus aculeatus*	S, U	Lindane***	44.0	-	Katz, 1961
Threespine stickleback, *Gasterosteus aculeatus*	S, U	Lindane***	50.0	47.0	Katz, 1961
Striped bass, *Morone saxatilis*	FT, U	Lindane***	7.3	7.3	Korn & Earnest, 1974
Pinfish, *Lagodon rhomboides*	FT, M	Lindane***	30.6	30.6	Schimmel, et al. 1977
Bluehead, *Thalassoma bifasciatum*	S, U	Technical lindane	14.0	14.0	Eisler, 1970
Striped mullet, *Mugil cephalus*	S, U	Technical lindane	66.0	66.0	Eisler, 1970
Northern puffer, *Sphaeroides maculatus*	S, U	Technical lindane	35.0	35.0	Eisler, 1970

Table 1. (Continued)

Species	Method*	Chemical	LC50/EC50 (µg/l)	Species Mean Acute Value (µg/l)	Reference
		BHC****			
Pink shrimp, Penaeus duorarum	FT, M	BHC	0.34	0.34	Schimmel, et al. 1977
Pinfish, Lagodon rhomboides	FT, M	BHC	86.4	86.4	Schimmel, et al. 1977

* S = static, FT = flow-through, M = measured, U = unmeasured

** EC50: decreased shell growth in oysters

*** Entom. Soc. Am. Reference Standard for lindane

****BHC (21% alpha BHC, 39% gamma BHC, 2.1% beta BHC, 23% delta BHC, 14.9% unidentified compounds)

Table 2. Chronic values for lindane (Macek, et al. 1976)

Species	Test[a]	Limits (µg/l)	Chronic Value (µg/l)
	FRESHWATER SPECIES		
Cladoceran, *Daphnia magna*	LC	11-19	14.5
Scud, *Gammarus fasciatus*	LC	4.3-8.6	6.1
Midge, *Chironomus tentans*	LC	2.2-5.0	3.3
Fathead minnow, *Pimephales promelas*	LC	9.1-23.5	14.6

[a] LC = life cycle or partial life cycle

Acute-Chronic Ratios

Species	Acute Value (µg/l)	Chronic Value (µg/l)	Ratio
Cladoceran, *Daphnia magna*	485	14.5	33
Midge, *Chironomus tentans*	207	3.3	63
Fathead minnow, *Pimephales promelas*	110[a]	14.6	7.5

[a] Estimated (see text)

Table 3. Species mean acute values and acute-chronic ratios for hexachlorocyclohexane

Rank[a]	Species	Species Mean Acute Value (ug/l)	Species Mean Acute-Chronic Ratio
	FRESHWATER SPECIES		
	Lindane		
22	Cladoceran, *Simocephalus serrulatus*	676	-
21	Cladoceran, *Daphnia magna*	485	33
20	Cladoceran, *Daphnia pulex*	460	-
19	Midge, *Chironomus tentans*	207	63
18	Goldfish, *Carassius auratus*	141.1	-
17	Guppy, *Poecilia reticulata*	138	-
16	Carp, *Cyprinus carpio*	90	-
15	Redear sunfish, *Lepomis microlophus*	83	-
14	Yellow perch, *Perca flavescens*	68	-
13	Fathead minnow, *Pimephales promelas*	67.1	7.5
12	Black bullhead, *Ictalurus melas*	64	-
11	Bluegill, *Lepomis macrochirus*	55.6	-
10	Scud, *Gammarus lacustris*	48	-

Table 3. (Continued)

Rank[a]	Species	Species Mean Acute Value (µg/l)	Species Mean Acute-Chronic Ratio
9	Coho salmon, Oncorhynchus kisutch	45	-
8	Brook trout, Salvelinus fontinalis	44	-
7	Channel catfish, Ictalurus punctatus	44	-
6	Chinook salmon, Oncorhynchus tshawytscha	40	-
5	Largemouth bass, Micropterus salmoides	32	-
4	Rainbow trout, Salmo gairdneri	32	-
3	Scud, Gammarus fasciatus	10.5	-
2	Sowbug, Asellus brevicaudus	10	-
1	Brown trout, Salmo trutta	2	-
	SALTWATER SPECIES		
	Lindane		
19	Polychaete, Neanthes arenaceodentata	3,680	-
18	American oyster, Crassostrea virginica	450	-
17	Sheepshead minnow, Cyprinodon variegatus	103.9	-
16	Striped mullet, Mugil cephalus	66.0	-

Table 3. (Continued)

Rank[a]	Species	Species Mean Acute Value (µg/l)	Species Mean Acute-Chronic Ratio
15	Mummichog, *Fundulus heteroclitus*	60.0	-
14	American eel, *Anguilla rostrata*	56.0	-
13	Threespine stickleback, *Gasterosteus aculeatus*	47	-
12	Northern puffer, *Sphaeroides maculatus*	35.0	-
11	Pinfish, *Lagodon rhomboides*	30.6	-
10	Striped killifish, *Fundulus majalis*	28.0	-
9	Bluehead, *Thalassoma bifasciatum*	14.0	-
8	Grass shrimp, *Palaemonetes vulgaris*	10.0	-
7	Atlantic silverside, *Menidia menidia*	9.0	-
6	Striped bass, *Morone saxatilis*	7.3	-
5	Mysid, *Mysidopsis bahia*	6.28	-
4	Hermit crab, *Pagurus longicarpus*	5.0	-
3	Sand shrimp, *Crangon septemspinosa*	5.0	-
2	Grass shrimp, *Palaemonetes pugio*	4.44	-

Table 3. (Continued)

Rank[a]	Species	Species Mean Acute Value (µg/l)	Species Mean Acute-Chronic Ratio
1	Pink shrimp, *Penaeus duorarum*	0.17	-
	BHC		
2	Pinfish, *Lagodon rhomboides*	86.4	-
1	Pink shrimp, *Penaeus duorarum*	0.34	-

[a] Ranked from least sensitive to most sensitive based on species mean acute value.

Final acute-chronic ratio for lindane = 25

Freshwater Final Acute Value for lindane = 2.2 µg/l

Revised Freshwater Final Acute Value for lindane (see text) = 2 µg/l

Freshwater Final Chronic Value for lindane = 2 µg/l ÷ 25 = 0.080 µg/l

Saltwater Final Acute Value for lindane = 0.16 µg/l

Table 4. Plant values for hexachlorocyclohexane

Species	Chemical	Effect	Result (µg/l)	Reference
		FRESHWATER SPECIES		
Alga, *Scenedesmus acutus*	Technical BHC	>20% growth inhibition in 5 days	1,000	Krishnakumari, 1977
Alga, *Scenedesmus acutus*	Alpha BHC	>20% growth inhibition in 5 days	500	Krishnakumari, 1977
Alga, *Scenedesmus acutus*	Beta BHC	>20% growth inhibition in 5 days	5,000	Krishnakumari, 1977
Alga, *Scenedesmus acutus*	Gamma BHC	>20% growth inhibition in 5 days	1,000	Krishnakumari, 1977
		SALTWATER SPECIES		
Natural phytoplankton communities	Lindane	28.5% decrease in productivity, ^{14}C	1,000	Butler, 1963
Alga, *Acetabularia mediterranea*	Lindane	Inhibition of cell growth and cell morphogenesis, reversible	10,000	Borghi, et al. 1973
Alga, *Chlamydomonas* sp.	Alpha BHC	No short-term (48-hr) toxic effect	Solubility limit (1,400)	Canton, et al. 1977
Alga, *Dunaliella* sp.	Alpha BHC	No effect on growth after 2 and 4 days	Solubility limit (1,400)	Canton, et al. 1978

Table 5. Residues for hexachlorocyclohexane

Species	Tissue	Lipid (%)	Chemical	Bioconcentration Factor	Duration (days)	Reference
			FRESHWATER SPECIES			
Zooplankton	Whole body	-	Lindane	336	5-60	Hamelink & Waybrant, 1976
Rainbow trout, Salmo gairdneri	Whole body	-	Lindane	486	108	Hamelink & Waybrant, 1976
Brook trout, Salvelinus fontinalis	Muscle	-	Lindane	70	261	Macek, et al. 1976
Fathead minnow, Pimephales promelas	Eviscerated	-	Lindane	477	304	Macek, et al. 1976
Bluegill, Lepomis macrochirus	Muscle	-	Lindane	35	735	Macek, et al. 1976
			SALTWATER SPECIES			
American oyster, Crassostrea virginica	All soft tissue	-	Technical BHC*	218	28	Schimmel, et al. 1977
Pinfish, Lagodon rhomboides	Edible tissue	-	Technical BHC*	130	28	Schimmel, et al. 1977
Pinfish, Lagodon rhomboides	Offal tissue	-	Technical BHC*	617	28	Schimmel, et al. 1977

* Technical grade BHC (21% alpha BHC, 39% gamma BHC, 2.1% beta BHC, 23% delta BHC, 14.9% unidentified compounds)

Maximum Permissible Tissue Concentration

Action Level	Concentration (mg/kg)	Reference
Frog legs	0.5	U.S. FDA Guideline 7420.08, 1978

Table 6. Other data for hexachlorocyclohexane

Species	Duration	Effect	Result (µg/l)	Reference
		FRESHWATER SPECIES		
		Lindane		
Scud, *Gammarus fasciatus*	48 hrs	LC50	39	Macek, et al. 1976
Rainbow trout, *Salmo gairdneri*	6 wks	Lethal threshold concentration	22	Tooby & Durbin, 1975
Brook trout, *Salvelinus fontinalis*	11 days	LC50	26	Macek, et al. 1976
Brook trout, *Salvelinus fontinalis*	261 days	Reduced growth	16.6	Macek, et al. 1976
Fathead minnow, *Pimephales promelas*	11 days	LC50	62	Macek, et al. 1976
Fathead minnow, *Pimephales promelas*	11 days	LC50	76	Macek, et al. 1976
Mosquitofish, *Gambusia affinis*	48 hrs	LC50	74	Culley & Ferguson, 1969
Bluegill, *Lepomis macrochirus*	21 days	LC50	29	Macek, et al. 1976
Bluegill, *Lepomis macrochirus*	21 days	LC50	31	Macek, et al. 1976
Chorus frog (tadpole), *Pseudacris triseriata*	96 hrs	LC50	2,700	Sanders, 1970
Toad (tadpole), *Bufo woodhousii*	96 hrs	LC50	4,400	Sanders, 1970
		alpha BHC		
Pond snail, *Lymnaea stagnalis*	48 hrs	LC50	1,200	Canton & Slooff, 1977

Table 6. (Continued)

Species	Duration	Effect	Result (µg/l)	Reference
Pond snail, *Lymnaea stagnalis*	40 days	EC50 egg production inhibition	250	Canton & Slooff, 1977
Pond snail, *Lymnaea stagnalis*	40 days	EC50 embryonic development	230	Canton & Slooff, 1977
Pond snail, *Lymnaea stagnalis*	40 days	Reproductive inhibition	65	Canton & Slooff, 1977
Cladoceran, *Daphnia magna*	25 days	EC50 reproduction	100	Canton, et al. 1975
		BHC		
Tubifex and *Limnodrilus* mixture	96 hrs	LC50	3,150	Whitten & Goodnight, 1966
Coho salmon, *Oncorhynchus kisutch*	48 hrs	LC50	200	Velson & Alderdice, 1967
Chinook salmon, *Oncorhynchus tshawytscha*	10 hrs	LC100	100	Anonymous, 1960
Rainbow trout, *Salmo gairdneri*	44.5 hrs	LC100	100	Anonymous, 1960
Goldfish, *Carassius auratus*	96 hrs	LC50	15,000	Henderson, et al. 1959
Fathead minnow, *Pimephales promelas*	96 hrs	LC50	15,000	Henderson, et al. 1959
Fathead minnow, *Pimephales promelas*	96 hrs	LC50	13,000	Henderson, et al. 1959
Guppy, *Poecilia reticulata*	96 hrs	LC50	14,000	Henderson, et al. 1959
Bluegill, *Lepomis macrochirus*	96 hrs	LC50	5,100	Henderson, et al. 1959
Toad (tadpole), *Bufo woodhousii*	96 hrs	LC50	3,200	Sanders, 1970

Table 6. (Continued)

Species	Duration	Effect	Result (µg/l)	Reference
		SALTWATER SPECIES		
		Lindane		
Grass shrimp, *Palaemonetes pugio*	4 days	Bioconcentration factor = 63	-	Schimmel, et al. 1977
Pink shrimp, *Penaeus duorarum*	4 days	Bioconcentration factor = 84	-	Schimmel, et al. 1977
Sheepshead minnow, *Cyprinodon variegatus*	4 days	Bioconcentration factor = 490	-	Schimmel, et al. 1977
Pinfish, *Lagodon rhomboides*	4 days	Bioconcentration factor = 218	-	Schimmel, et al. 1977
Longnose killifish, *Fundulus similis*	48 hrs	LC50	240	Butler, 1963
White mullet, *Mugil curema*	48 hrs	LC50	30	Butler, 1963
Brown shrimp, *Penaeus aztecus*	48 hrs	EC50*	0.40	Butler, 1963
		alpha BHC		
Alga, *Chlamydomonas*	2 hrs	f 310**	10	Canton, et al. 1977
Alga, *Chlamydomonas*	2 hrs	f 2,700**	1,000	Canton, et al. 1977
Alga, *Dunaliella*	2 hrs	f 1,500**	1,000	Canton, et al. 1977
		BHC***		
Pink shrimp, *Penaeus duorarum*	4 days	Bioconcentration factor = 80	-	Schimmel, et al. 1977
Pinfish, *Lagodon rhomboides*	4 days	Bioconcentration factor = 482	-	Schimmel, et al. 1977

Table 6. (Continued)

Species	Duration	Effect	Result (µg/l)	Reference
		Tri-6 Dust No. 30****		
Brown shrimp, Penaeus aztecus	24 hrs	LC50	35	Chin & Allen, 1957
White and brown shrimp, Penaeus setiferus Penaeus aztecus	24 hrs	LC50	400	Chin & Allen, 1957

* EC50 - loss of equilibrium in brown shrimp.

** f-Freundlich isotherm: concentration (alpha BHC) in algae (µg/g)/concentration (alpha BHC) in water phase (µg/ml).

*** Technical grade BHC (21% alpha BHC, 39% gamma BHC, 2.1% beta BHC, 23% delta BHC, 14.9% unidentified compounds).

****Tri-6 Dust No. 30 (3.0% gamma BHC, 5.1% other isomers BHC, 91.9% inert). Result based on µg/l Tri-6 Dust No. 30.

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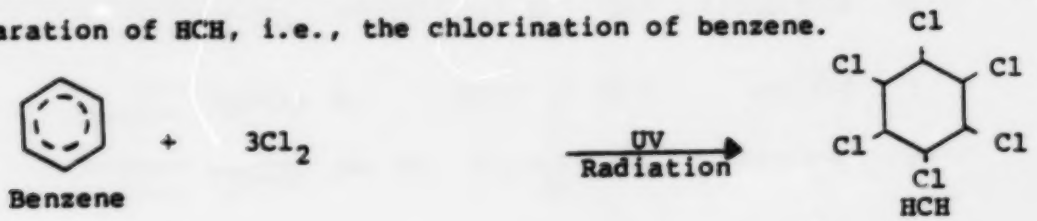
Mammalian Toxicology and Human Health Effects

INTRODUCTION

Hexachlorocyclohexane (HCH) was first synthesized in 1825 by Faraday. The insecticidal properties of HCH were demonstrated by the American chemist Bender in 1933 and later by the French chemist Dupire in 1940. One of the common names for HCH is BHC (benzene hexachloride). This is obviously a misnomer since HCH is a saturated chlorinated hydrocarbon and, therefore, has no aromaticity. The common misnomer, BHC, probably came from the original method of preparation of HCH, i.e., the chlorination of benzene.



This preparation method yields technical grade HCH which is a mixture of the five basic isomers (see Figure 1). The composition of technical HCH is approximately as follows:

Isomer		Percent
alpha	(α)	60-70
beta	(β)	5-12
gamma	(γ)	10-15
delta	(δ)	6-10
epsilon	(ϵ)	3-4

The gamma-isomer (γ-HCH) has the lowest melting point (112.8°C) and the highest acute toxicity and is commonly called lindane.

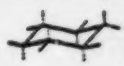
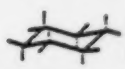
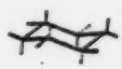
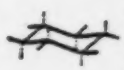
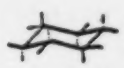
Isomer	% in techn. BHC	Melting point	Vapour pressure mmHg 20 °C	Polarity	Refraction index nD 20	Wave length in angstroms	Configuration Cl — H	Crystal
α	60-70	157,5-158,5	0,02	2,22:	1,60 -1,626	1258		monoclinic prisms
β	5-12	309	0,005	0	1,630	1346		cubic (octahedral)
γ	10-15	112,8	0,03	2,8: 3,6	1,60 -1,635	1322		monoclinic crystals
δ	6-10	138-139	0,02	2,2: (2,17: 2,32)	1,576-1,674	1181		crystals or fine platelets
ε	3- 4	218,8		0	1,00 -1,635	1396		monoclinic needles or
ζ		68 - 88						hexagonal
η		89,8- 90,5						monoclinic
θ		124 -125						crystals

FIGURE 1

Comparison of the Physical Constants of Lindane and some of the other BHC Isomers

Source: Ulmann, 1972

Lindane, named after the Belgian chemist, van der Linden, has been marketed under a number of trade names as an insecticide including the following registered trademarks:

Jacutin	(emulsifiable concentrate)
Lindafor 90	(wettable powder)
Lindamul 20	(emulsifiable concentrate)
Nexit-Staub	(0.8 percent dust)
Prodactic	(wettable powder)

Other names for γ-HCH include γ-BHC, γ-lindane, purified BHC, and technical lindane. The common names in Sweden, Denmark, and the USSR are hexaklor, 666, and hexachloran, respectively. It is important to recognize the various synonyms for HCH and its isomers due to the extensive use and misuse of these names in the literature. In this document, HCH will be used as an abbreviation for hexachlorocyclohexane and its synonyms. However, the various isomers will be designated by the appropriate Greek letter. Lindane will be referred to as γ-HCH. The technical product will be t-HCH.

The major commercial usage of HCH is based upon its insecticidal properties. As indicated previously, the γ-isomer has the highest acute toxicity, but the other isomers are not without activity. It is generally advantageous to purify the γ-isomer from the less active isomers. The γ-isomer acts on the nervous system of insects, principally at the level of the nerve ganglia (Block and Newland, 1974). As a result, lindane has been used against insects in a wide range of applications including treatment of animals, buildings, man for ectoparasites, clothes, water for mosquitoes, living plants, seeds and soils. Some applications have been abandoned due to excessive residues, e.g., stored foodstuffs.

EXPOSURE

Ingestion from Water

The contamination of water with HCH has occurred principally from two sources:

(1) direct application of γ-HCH or technical HCH to aquatic systems for the control of mosquitoes

(2) the use of HCH in agriculture and forestry.

The contamination of water supplies from agriculture and forestry comes usually from HCH associated with soil or sediment particles (Lotse, et al. 1968). The only other major source of aquatic pollution of HCH occasionally occurs during its manufacture. HCH-containing waste water can be generated during the synthesis, crystallization, and isomer separation. These HCH contaminated wastewaters are usually cleaned up prior to discharge, but occasionally some contamination occurs.

The occurrence of HCH in water supplies is potentially more of a problem than for many other organochlorine insecticides, such as DDT, endrin, aldrin, heptachlor, etc., due to HCH's high water solubility. Solubility of γ-HCH is 7.3 mg/l at 25°C, 12 mg/l at 35°C, and 14 mg/l at 45°C (Gunther, et al. 1968). However, the different HCH isomers exhibit different solubilities at a constant temperature, e.g.,

	Sol. @ 30°C	Vapor Pressure*
alpha	10 mg/l	0.06 torr
beta	5 mg/l	0.17 torr
gamma	10 mg/l	0.14 torr

*Source: National Academy of Sciences (NAS), 1975

γ-HCH has been detected in the finished water of Streator, Illinois at 4 µg/liter (U.S. EPA, 1975). γ-HCH has a low residence time in the aquatic environment and the principal routes by which γ-HCH disappears are sedimentation, metabolism, and volatilization. γ-HCH is generally found to contribute less to aquatic pollution than the other HCH isomers (Henderson, et al. 1971).

Ingestion from Food

Duggan and Duggan (1973) tabulated the human daily intake for γ-HCH and other HCH isomers. For γ-HCH the daily intake was 1 to 5 µg/kg body weight/day and was 1 to 3 µg/kg/day for all other isomers of HCH. Assuming a 70-year lifespan for a 70 kg man, his lifetime ingestion would be 1.8 to 8.9 grams of γ-HCH, and 1.8 to 5.4 grams of all other isomers of HCH. Engst, et al. (1976) in a study of German citizens, determined that a male of 65 kg would consume 0.25 mg of γ-HCH in 70 years. Reasons for the large difference in the two investigations are apparently due to exposure and consumption of fish products.

The chief sources of HCH residues in the human diet are milk, eggs, and other dairy products. Seafood as a source of HCH for humans is usually minor, which may be attributed to the relatively high rate of dissipation of HCH in the aquatic environment. γ-HCH and other HCH isomer residues have generally been of low order of magnitude.

A bioconcentration factor (BCF) relates the concentration of a chemical in aquatic animals to the concentration in the water in which they live. The steady-state BCFs for a lipid-soluble compound in the tissues of various aquatic animals seem to be proportional to the percent lipid in the tissue. Thus the per capita

ingestion of a lipid-soluble chemical can be estimated from the per capita consumption of fish and shellfish, the weighted average percent lipids of consumed fish and shellfish, and a steady-state BCF for the chemical.

Data from a recent survey on fish and shellfish consumption in the United States were analyzed by SRI International (U.S. EPA, 1980). These data were used to estimate that the per capita consumption of freshwater and estuarine fish and shellfish in the United States is 6.5 g/day (Stephan, 1980). In addition, these data were used with data on the fat content of the edible portion of the same species to estimate that the weighted average percent lipids for consumed freshwater and estuarine fish and shellfish is 3.0 percent.

No measured steady-state bioconcentration factor (BCF) is available for hexachlorocyclohexane or any of its isomers, but the equation "Log BCF = (0.85 Log P) - 0.70" can be used (Veith et al., 1979) to estimate the BCF for aquatic organisms that contain about 7.6 percent lipids (Veith, 1980) from the octanol-water partition coefficient (P). Based on an average measured log P value of 3.80 (Hansch and Leo, 1979), the steady-state bioconcentration factor for hexachlorocyclohexane is estimated to be 339. An adjustment factor of 3.0/7.6 = 0.395 can be used to adjust the estimated BCF from the 7.6 percent lipids on which the equation is based to the 3.0 percent lipids that is the weighted average for consumed fish and shellfish. Thus, the weighted average bioconcentration factor for hexachlorocyclohexane and the edible portion of all freshwater

and estuarine aquatic organisms consumed by Americans is calculated to be 339 x 0.395 = 130.

Inhalation

Little is known about the concentration and distribution of γ-HCH in the atmosphere. Abbott, et al. (1966) found only traces of HCH in air in central and suburban London. According to an investigation by Barney (1969) the γ-HCH intake by inhalation is 0.002 µg/kg/day, while the FAO/WHO acceptable daily intake (A.D.I.) limit is 1 µg/kg/day (NAS, 1977). Hesse, et al. (1976) showed that short-term inhalation of HCH by men did not lead to a significant increase of the compound in the blood and urine and had no influence on serum enzymes either immediately or within 21 to 24 days after exposure. Voitenko (1978) described a synergistic action for γ-HCH administered through both the gastrointestinal (1.5 mg/kg/day) and respiratory (0.84 mg/m^3) tracts for four months in albino rats.

Dermal

γ-HCH has been used in human and veterinary dermatology against ectoparasites for more than 25 years. Many publications express good dermal tolerance and there is little mention of adverse skin reaction. In a few cases, dermal reactions after contact with γ-HCH preparations have been described as local irritation and an occasional case of eczema has been described. The adverse experiences with man have usually been with concentrated liquid formulations. All these reactions healed after scab formation.

PHARMACOKINETICS

Absorption

The rapidity of γ-HCH absorption is enhanced by lipid mediated carriers. For an organochlorine insecticide, lindane is unusually soluble in water, another factor contributing to its rapid absorption and excretion (Herbst and Bodenstein, 1972).

Fisher 344 rats were treated with daily oral injections of peanut oil spiked with γ-HCH which was ^{14}C-labeled. For 2 mg administered orally, only 0.1 to 4 µg γ-HCH was found in the urine, representing 0.005 to 0.2 percent of the administered γ-HCH. However, 2 to 5 percent of the original γ-HCH was found in the feces (Chadwick, et al. 1971, 1978). It can be concluded from these data that γ-HCH is not generally excreted in the urine but is in the feces. Excretion from the feces, however, comprises only a small percentage of the original orally administered dose.

An oil solution containing 40 mg γ-HCH per kg body weight was injected intraperitoneally to rats, resulting in 35 percent absorption. At the end of a 24 hour period, 10 percent of the original amount still remained in the abdominal cavity (Koransky, et al. 1963). Low lindane levels in the intestinal wall indicated a very rapid absorption process.

Ginsburg, et al. (1977) studied the dermal absorption of lindane in infants and children. Twelve children with infection caused by Sarcoptes scabiei and eight noninfected siblings for whom prophylactic γ-HCH had been prescribed were included in the investigation. Blood specimens were obtained at 2, 4, 6, 8, 12, 24, and 48 hours after the topical application of one percent γ-HCH lotion. γ-HCH was detected in the blood at all times, with

peak concentration noticed six hours after application. An absorption half-life of 17.9 hours in the blood of infected children was recorded and 210.4 hours in children with normal skin. These findings support previous observations in animals and adult human volunteers that lindane is absorbed through the skin.

Distribution

γ-HCH has reached detectable levels in the brain, liver, skin, and musculature of mice in as little as three hours after administration (van Asperen, 1958). Carbon-14 tagged γ-HCH administered to rats intraperitoneally in a dose of 14 mg/kg body weight was noticed very quickly in the fatty tissues. At least 75 percent of the labeled γ-HCH was consistently found in the skin, muscle, and fatty tissue (Koransky, et al. 1963). Another experiment utilizing ^{14}C-labeled HCH isomers revealed a uniform distribution in adipose tissue throughout the body of mice (Nakajima, et al. 1970). On the other hand, concentration of γ-HCH in the brain at a level higher than other organs is supported in the literature (Laug, 1948; Davidou and Frawley, 1951; Koransky, et al. 1963; Huntingdon, 1972).

A 17 mg/kg body weight dose of lindane in rape oil given orally to calves showed a 0.62 mg/l blood level after three hours, 2.0 mg/l after 24 hours and 0.124 mg/l after seven days. Only barely detectable levels were found at three and six weeks subsequent to application (Kadis and Jonasson, 1965).

γ-HCH has also been noted to enter the fetus through the placenta. Residue levels of various pesticides, including lindane, were found in the fatty tissue of pregnant women and in the vernix

caseosa of their newborn babies. In some women with a normal course of pregnancy, pesticide concentrations were extraordinarily high, but did not cause premature termination of the pregnancy or noticeably affect intrauterine fetal development (Poradovsky, et al. 1977). Analysis of macroscopically normal appearing human embryos and fetuses obtained from abortion cases revealed detectable levels of β-HCH (Nishimura, et al. 1977). Higher concentrations were found in the skin than in the brain. Levels in the skin of more highly developed fetuses were greater as a result of a more highly developed skin fat content. Concentration never exceeded the corresponding values of normal adult organs.

In an accidental case of human poisoning, 0.29 mg/l γ-HCH was found in the blood plasma during the convulsive phase, and decreased to a 0.02 mg/l level seven days later (Dale, et al. 1967). Several authors have reported on the level of γ-HCH in human milk (Savage, et al. 1973; Curley and Kimbrough, 1968). Bakken and Siep (1977) found that approximately 56 percent of those persons examined in Norway showed milk levels of HCH greater than the maximum approved concentration for cows' milk by the World Health Organization.

Metabolism

The biological transformation of various hexachlorocyclohexane isomers in mammals results in the formation of various chlorophenols including: 2,4,5- and 2,3,5-trichlorophenol; 2,3,4,5-tetrachlorophenol; 2,4,6-trichlorophenol; 3,4-dichlorophenol; 2,3,4,6-tetrachlorophenol; 2,3,4,5,6-pentachloro-2-cyclohexene-1-ol (PCCOL); and 3,4-dichlorophenylmercapturic acid. These are

commonly excreted in the urine as conjugates of sulfuric and glucuronic acid (Grover and Sims, 1965; Freal and Chadwick, 1973; Chadwick and Freal, 1972). These metabolites have been found in the blood, liver, kidneys, spleen, heart, and brain of rats fed γ-HCH, but were not detected in the intestine or feces (Engst, et al. 1976). Freal and Chadwick (1973) originally suggested γ-HCH is metabolized in the rat to a series of metabolites ranging from pentachlorocyclohexenes to trichlorobenzenes that result in chlorophenols. Chadwick, et al. (1975) later demonstrated that γ-HCH undergoes metabolism to an intermediate hexachlorocyclohexene, from which further degradation yields PCCOL, two tetrachlorophenols and three trichlorophenols. This metabolic pathway was not observed for the other hexachlorocyclohexane isomers. Freal and Chadwick (1973) also noted an enhanced metabolism of γ-HCH upon pretreatment with the other BHC isomers. This enhancement decreased in the order of alpha-delta-gamma-beta. DDT, Mirex®, chlordane, and HCB also stimulate the metabolism of γ-HCH significantly (Chadwick, et al. 1977a). The preapplication of γ-HCH has also been shown to stimulate its own biodegradation in rats (Noack, et al. 1975).

Pretreatment of male Wistar rats with cadmium also has been noted to alter γ-HCH metabolism. Three days after exposure to ^{14}C γ-HCH, the control rats excreted significantly more radioactivity than the Cd-treated groups. Cd-exposure altered the distribution of neutral and polar γ-HCH metabolites, as well as inhibiting the dehydrogenation of γ-HCH to hexachlorocyclohexene (Chadwick, et al. 1978).

The administration of dimethyl sulfoxide with γ-HCH to female rats led to impaired γ-HCH metabolism and lowered specific microsomal phospholipid content indicated some interaction between γ-HCH, dimethyl sulfoxide, and dietary lipids (Chadwick, et al. 1977b).

Dietary fibers are known to have protective effects against a variety of chemical toxicants through metabolic alterations. Chadwick, et al. (1977c) demonstrated that rats fed diets supplemented with fiber showed a higher dehydrogenation and dechlorination of γ-HCH and suggests a substantial alteration in the excretion and metabolism of γ-HCH and its metabolites in mammals.

Trichlorophenols also result from the metabolism of isomers other than γ-HCH, although it seems that tetrachlorophenols are not produced. The excretion of mercapturic acid conjugates has also been noted (Kurihara, 1979). Using rat liver preparation, Portig, et al. (1973) detected the direct glutathione dependent conversion of α-HCH. Eliminated products of HCH metabolism, both free and conjugated chlorophenols, are far less toxic, however, than the parent compounds (NAS, 1977). A proposed degradation scheme is shown in Figure 2 (Chadwick, 1975).

Excretion

Continual administration of γ-HCH to an organism will lead to an equilibrium concentration and stabilization. This equilibrium concentration occurs as continuing intake is offset by degradation and elimination of the γ-HCH.

Kitamura, et al. (1970) has investigated the rate of elimination of γ-HCH as compared to β-HCH. Figure 3 shows that β-HCH is

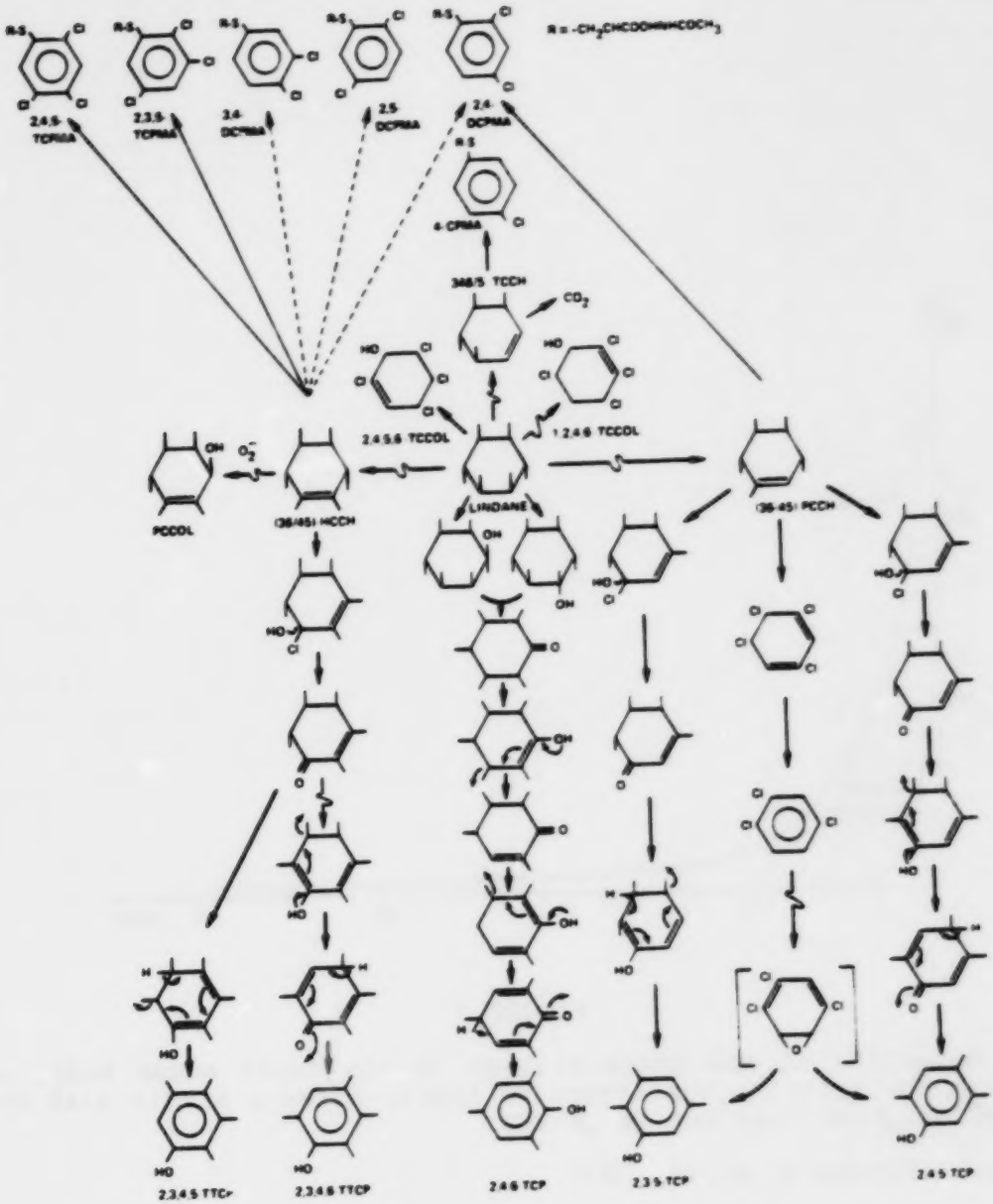


FIGURE 2

Metabolism of Lindane

Source: Chadwick, et al. 1975

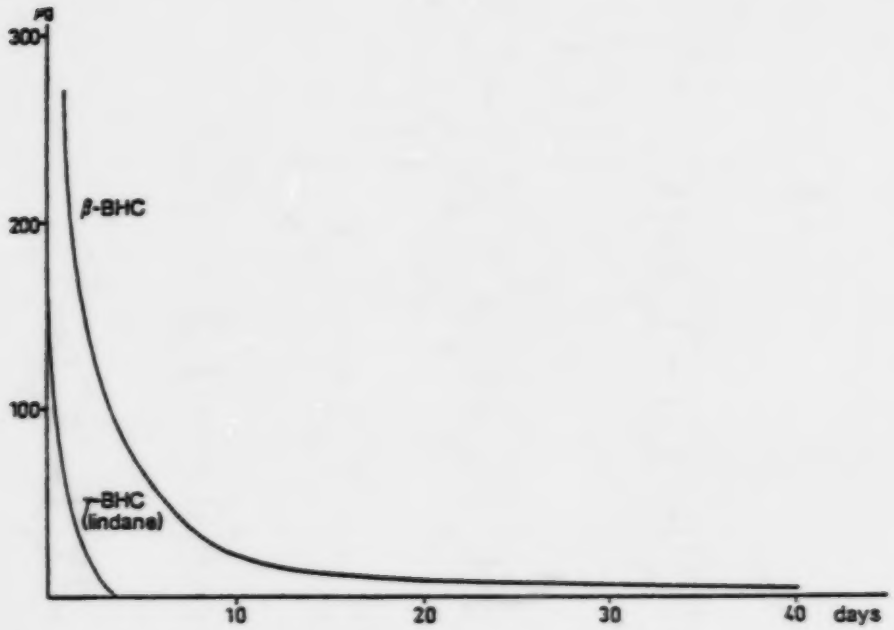


FIGURE 3

Reduction of HCH concentration in the total mouse body, excluding the skin and the digestive tract, after a single oral dose of 500 µg γ-HCH and 500 µg β-HCH.

Source: Kitamura, et al. 1970

excreted at a much slower rate. Since the pure β-isomer seems to persist in the body, there is justification for the use of only the pure form of the γ-isomer in situations that might lead to absorption. The rapid biological deterioration of γ-HCH is self-induced and minimizes the health hazards presented by hexachlorocyclohexanes (Sieper, 1972; Chadwick, et al. 1971; Chadwick and Freal, 1972).

Even prolonged γ-HCH administration results in complete elimination when application has been terminated. In one experiment a γ-HCH concentration in rat fatty tissues of 102 ppm was achieved. One week subsequent to cessation of administration, the concentration had dropped to zero (Frawley and Fitzhugh, 1949). Similar results have been obtained, for example, a concentration of 281 ppm in fatty tissue was eliminated within two weeks (Lehman, 1952a,b). Three days after rats were fed a diet containing 100 mg/kg of γ-HCH over a ten day period, it was found that quantities in the body had diminished to 0.1 ppm. Similarly, 24 hours after cessation of feeding rats a diet containing 10 mg/kg γ-HCH for 20 days, no residue could be detected using gas chromatography with an electron capture detector (Kitamura, et al. 1970).

Only very slight amounts of unaltered γ-HCH are excreted. Dietary intake by rats for one month revealed that only about four percent had been eliminated in the urine by the end of feeding period (Laug, 1948). No excretory traces of unchanged lindane have been noticed with intraperitoneal injections. The main excretory products in urine are water soluble glucuronides, mercapturic acid conjugates, and sulfates. Single oral administrations to rats of

50 to 100 mg lindane per kg body weight resulted in 1.5 mg per day increase of urinary glucuronic acid excretion within about two weeks. Organic sulfur compound excretion was enhanced by about 35 to 58 percent (Rusiecki and Bronisz, 1964). When given at 20 mg/kg body weight, an increase in glucuronic acid excretion was noticed after two days (Chadwick, et al. 1971; Chadwick and Freal, 1972).

HCH is eliminated not only by urinary excretion, but also via milk secretion. It commonly exists in low concentrations in human milk. Usually the β-isomer accounts for 90 percent of the HCH present. The α- and γ-isomers account for the remaining 10 percent (Herbst and Bodenstein, 1972).

EFFECTS

Acute, Subacute, and Chronic Toxicity

Of the various isomers of HCH, γ exhibits the greatest acute toxicity to mammalian organisms. This toxicity varies with the species subject. Toxicity also varies with route of administration. Intravenous administration produces the most severe injury, followed by intraperitoneal, subcutaneous, oral and then dermal (Shirakowa, 1958). As a general rule, formulations of HCH in oil and fat are associated with higher toxicities; the least toxic form is the pure crystalline chemical. Variations in toxicity are also noted among different types of oils or solvents (Starek and Zabinski, 1970).

It has been demonstrated that young animals are more sensitive to the toxic effects of γ-HCH than adults of the same species (Shirakowa, 1959; Radaleff and Bushland, 1960). The increased sensitivity of young mammals to intoxication, at least to the age of

weaning, is a result of low production of liver enzymes affecting detoxification at an early age (Fouts and Adamson, 1959). Diseased and distressed animals show a similar sensitivity (Chen, 1968).

γ-HCH has a higher acute toxicity than many other chlorinated hydrocarbons since absorption is rapid; and visible clinical symptoms quickly develop (Lehman, 1951). This rapid uptake as well as a higher water solubility account for the narrow range between lowest toxic and lethal doses of γ-HCH relative to similar compounds like DDT (Gunther, et al. 1968; Martin, 1971).

A case of acute poisoning with γ-HCH in a 42-year-old male worker revealed an array of symptoms: depression, headache, emesis, asthenia, epileptiform attacks, sleeplessness, profuse perspiration, pathologically increased tendon reflex, tremor of the fingers, oral automatism, bilateral Marinesiu-Radovici reflex, Romberg's sign, and Hoffmann's and Troemmer's signs in the upper extremities. Several weeks after poisoning the blood contained γ-HCH between 0.1 and 0.5 mg/l, and the cerebrospinal fluid contained 0.2 mg/l γ-HCH. This patient was therapeutically treated with barbituates, sedatives, glucose, and vitamins C and B_{12}, which elicited a favorable response (Pernov and Kyurkchiyev, 1974).

Another case describes a 35-year-old man who ingested γ-HCH contaminated food. Grand mal seizures which recurred for nearly two hours, developed rapidly as well as severe acidemia. Muscle weakness and pain, headaches, episodic hypertension, myoglobinuria, acute renal failure and anemia were also seen. Pancreatitis developed on the 13th day after ingestion, and on the 15th day, a muscle biopsy revealed widespread necrosis and muscle fiber

regeneration. Characteristic symptoms which occurred during the year following exposure included recent-memory loss, loss of libido, and easy fatigability (Munk and Nantel, 1977). Topical application of δ-HCH in a child caused irritability and hyperactivity (Wheeler, 1977). Subsequent accidental oral administration of γ-HCH induced sporadic vomiting. Central nervous system stimulation seems to be the major toxic function of HCH, regardless of the absorption mechanism (Wheeler, 1977). This manifestation is of primary clinical importance. In most animals, initial symptoms of poisoning include an aggressive and excited state. Some cases of accidental acute γ-HCH poisoning in man by oral intake are shown in Table 1.

Alterations in liver function are also significant toxic effects of HCH. Rats fed both the β- and γ-isomers showed an increase in alanine aminotransferase, and a decrease in aspartate aminotranferase, alkaline phosphatase, and acid phosphatase (Srinivasan and Radhakrishnamurty, 1977). After short-term oral administration of γ-HCH to rats, (5 to 20 mg/kg), an increase in the ascorbic acid in the urine and blood serum was noted. Electron microscopy revealed an increase in smooth endoplasmic reticulum in liver hepatocytes of the intermediary zone. Free ribosomal increase was probably related to the intensified formation of microsomal protein. Individual cell glycogen content was also observed and explained by increased glucuronic and ascorbic acid syntheses (Herbst, et al. 1974). Histochemical studies following daily administration of 7.5 mg of the γ-isomer to albino rats revealed disturbances in the carbohydrate metabolism-activation-lytic

TABLE 1

Accidental Acute γ-HCH Poisoning in Man
(oral intake)

Persons Involved	Age	Dose (mg/kg)	Fatal cases	Formulation Involved	Remarks
10	adults & children	up to 300	3	50% WP	7 survived on therapy
1	adult	ca. 90	-	20% EC	survived on therapy
11	adults	ca. 10	-	crystalline in coffee	survived on therapy
8	children	?	4	highgrade BHC (?) (p.o. + p.c. + inhal.)	4 survived on therapy all undernourished
1	child	(?) ca. 30	-	dust formulation	no symptoms
7	children	ca. 50-120	-	smoke sticks	survived on therapy
6	children	ca. 6-80	-	smoke sticks	survived on therapy
3	children	up to 65	-	smoke sticks	survived on therapy
5	adults	?	4	in alcohol	1 survived on therapy
2	infants	?	2	smoke sticks	-
3	children	?	-	smoke tablets	survived on therapy
2	adults	?	1	20% EC	survived on therapy
1	child	?	1	½ smoke tablet	-
1	child	?	-	10% or 20% EC	no therapy, severe after effects
5	adults	?	-	powder in pudding	survived on therapy
1	-	?		vermicide tablets	undernourished, survived on therapy
1	child	?	1	smoke tablet	-
1	child	?	-	?	survived on therapy
1	child	?	1	4-5 smoke tablets	-
1	child	?	1	½ smoke tablet	-
4	1 child, 3 adults	?	-	1 x inhalation 4 x p.o.	1 x urticaria, all survived on therapy
5	?	1 x 48 4 x ?	-	? ?	-
1	adult	152	-	crystalline, dust	survived on therapy
1	child	?	-	smoke tablets	survived on therapy

*Source: Ulman, 1972

processes (Shilina, 1973). γ-HCH may also modify the metabolism of drugs in the liver (Vrochinskii, et al. 1976).

Dikshith, et al. (1978) gave daily dermal applications of HCH to guina pigs in 100, 200, and 500 mg/kg doses for 30 days. No mortality occurred in response to the 100 mg/kg/day, but significant pathologic and biochemical changes occurred in the vital organs. Massive congestion and thickened blood vessels were seen in the livers of the animals treated with 100 mg HCH as compared to the controls. Biochemically, the activity of glutamic oxaloacetic transaminase, glutamic pyruvic transaminase, and alkaline phosphatase in the liver and serum revealed significant changes from that of the controls. All animals exposed to the high doses (200 and 500 mg) died within 5 to 12 days.

Hexicid® (1 percent γ-HCH) is highly effective in the treatment of scabies. Toxic side effects with irritation of the central nervous system have been reported after improper or prolonged use (Lee, et al. 1976). Side effects have included nausea, vomiting, spasms, weak respiration with cyanosis, and blood dyscrasia. The skin absorption of γ-HCH has been shown to be in the order man < pig < rat < rabbit; the permeability characteristics of pig skin were closest to that of man (Bartek and LaBudde, 1975).

Extensive data regarding the chronic toxicity of γ-HCH to rats were compiled by several investigators in the early 1950s (Fitzhugh, et al. 1950; Lehman, 1952a,b). These studies involved the administration of γ-HCH in the crystalline form at 0, 10, 100, and 800 mg/l, and as an oil solution at 0, 5, 10, 50, 100, 400, 800, and 1,600 mg/l. No clinical or pathological changes were detected

at levels of 400 mg/l or lower; however, liver weight increase was noticed at 100 mg/l, particularly with respect to the oil forms. This was a dose-related effect and increased with concentration. At higher doses, liver cell hypertrophy (fat degeneration and necrosis) and nephritic changes were noted. Oil solution concentrations of 400, 800, and 1,600 mg/l decreased lifespan by 20 to 40 percent, although a concentration of 800 mg/l crystalline form did not yield similar effects.

Inhalation of δ-HCH by rats for varying times resulted in little or no organ alterations. For example, inhalations of 0.78 mg/m^3 for seven hours, five days a week for 180 days showed some liver cell enlargement although no clinical symptoms were noticed. Two out of 20 rats exposed to three percent δ-HCH dust for seven hours a day, five times a week for 218 days developed some doubtful liver and kidney changes (Heyroth, 1952). As a result of these and other inhalation experiments, the United States and most western countries, in 1954 established a maximum allowable air concentration of 0.5 mg/m^3 (Ball, 1956).

The addition of δ-HCH at 10 mg/kg to the diet of rats for one to two years revealed noxious effects to them and their offspring. Body weight decreased after five months of administration, and increased ascorbic acid levels in the urine along with changes in the ascorbic acid levels of the blood were noted. Ascorbic acid was decreased in both the liver and adrenals (Petrescu, et al. 1974). Experimental data regarding the toxicity of various isomers of HCH are shown in Table 2.

TABLE 2

Toxicity of HCH Isomers*

Chemical Form and Animal Species	Duration of Study	Dosage Levels (mg/kg/diet) and No. of Animals Per Group	Highest No-Adverse-Effect Level or Lowest-Minimal-Effect Level mg/kg in the diet	Effect Measured
Rat				
t-HCH	approx. 2 yr	10, 50, 100, 800 (10 M, 10 F)	800	reduced lifespan, no
α-HCH, -HCH	approx. 2 yr	10, 50, 100, 800 (10 M, 10 F)	800	increased tumor in-
γ-HCH	approx. 2 yr	5, 10, 50, 100, 400, 800, 1,600 (10 M, 10 F)	800	cidence
γ-HCH	2 yr	25, 50, 100	100	no increase in tumor incidence
α-HCH	78 weeks	500, 1,000, 1,500 (18-24 M)	500	liver hypertrophy (nodular hyperplasia, carcinoma at 1,000 and 1,500)
β-HCH	78 weeks	500, 1,000	500	liver hypertrophy
γ-HCH	78 weeks	500	500	liver hypertrophy
δ-HCH	78 weeks	500, 1,000	1,000	liver hypertrophy
Mouse				
t-HCH	24 weeks	6.6, 66, 660 (20 M, dd strain)	660	hepatoma (20/20)
α-HCH	24 weeks	100, 250, 500 (20 M, dd strain)	250	hepatic nodules (9/20), tumors at 500 (20/20)
β-HCH	24 weeks	100, 250, 500 (20 M, dd strain)	500	no adverse effect
γ-HCH	24 weeks	100, 250, 500 (20 M, dd strain)	500	no adverse effect
β-HCH	110 weeks	200 (30 M, 30 F; CPI strain)	200	hepatic tumors, lung metastases
δ-HCH	110 weeks	400 (29 M, 29 F; CPI strain)	400	hepatic tumors, lung metastases
t-HCH	26 weeks	600 (20 M; ICR-JCL strain)	600	hepatic nodules, tumors
α-HCH	26 weeks	600 (20 M; ICR-JCL strain)	600	hepatic tumors, lung metastases
β-HCH	26 weeks	600 (20 M; ICR-JCL strain)	600	hepatic tumors, lung metastases
δ-HCH	26 weeks	600 (20 M; ICR-JCL strain)	600	hepatic tumors, lung metastases
γ-HCH	26 weeks	300, 600	300	no adverse effect
α-HCH	24 weeks	50, 100, 250 (30 M, dd strain)	100	liver hypertrophy (hyper-plasia, tumors at 250)
β-HCH	24 weeks	50, 100, 250 (30 M, dd strain)	250	liver hypertrophy
γ-HCH	24 weeks	50, 100, 250 (30 M, dd strain)	250	liver hypertrophy (slight)
γ-HCH	80 weeks	12.5, 25, 50 (NMRI strain)	50	no adverse effect

The above compounds are animal carcinogens.
*Source: NAS, 1977

Male and female beagle dogs were fed γ-HCH at concentrations of 25, 50, and 100 mg/kg in the diet for 104 weeks. Friable and slightly enlarged livers were noted at 100 mg/kg/diet, but no histopathological changes were noticed. The negative findings at 50 mg/kg/diet are consistent with a no-effect level for this species (Rivett, et al. 1978). The no-effect levels after chronic poisoning to several other mammals are shown in Table 2.

Kazakevich (1974) has reported that production workers with exposure to t-HCH have exhibited a variety of symptoms including headache, vertigo, irritation of the skin, eyes and respiratory tract mucosa, etc. In some instances, there were apparent disturbances of carbohydrate and lipid metabolism. Dysfunction of the hypothalamo-pituitary-adrenal system was also reported by the authors. Besughyi, et al. (1973) reported similar findings in 88 persons having headache, vertigo, and irritation of the skin, eyes and respiratory tract mucosa.

A study involving 59 females and 29 males with occupational exposure to HCH for periods ranging from 11 to 23 years revealed biochemical manifestations of toxic hepatitis. Fifty-five percent of the workers showed pathological changes in the hepatobiliary system, 33 percent of the total being chronic hepatitis, and 5 percent being chronic pancreatitis. Some form of biochemical abnormality was noted in 60 percent of all cases (Sasinovich, et al. 1974).

Synergism and/or Antagonism

The daily treatment of beagle dogs with phenobarbital for 60 days prior to the administration of γ-HCH brought about a

reduction of γ-HCH concentrations in the brain. The control dogs (without pretreatment) were found to convulse after 27 minutes of i.v. infusion of 7.5 mg γ-HCH/minute, while the phenobarbital-pretreated group did not convulse within 60 to 70 minutes. By the end of the infusion period, the phenobarbital pretreated group showed significantly higher concentration of blood γ-HCH. As compared with the control group, the brains of the phenobarbital pretreated group contained a much smaller amount of the total γ-HCH administered. It seems that phenobarbital pretreatment leads to decreased convulsion effect of γ-HCH (Litterst and Miller, 1975).

Various substances have been found to have antagonistic effects on γ-HCH poisoning and offer potential as treatment or antidotes. The administration of silymarin to γ-HCH-intoxicated mice resulted in a prolonged survival time (Szpunar, et al. 1976). An oral application mixture of HCH and Rogor® at concentrations of 3.2 and 3.8 mg/kg body weight to rabbits for a three month period re sulted in disruption of lipid metabolism and a decreased serum cholesterol/lecithin ratio. However, methionine, galascorbin, and vitamin B_{12}, individually aided the recovery of disrupted lipid metabolism, although a combination of the three was more effective (Karimov, 1976). Alterations in the serum cholestrol levels may be indicative of chronic poisoning by these pesticides.

Pretreatment of Wistar rats with γ-HCH has revealed a reduction in the teratogenic effect of some compounds. Preliminary treatment weakened the teratogenic and embryotoxic action of a carbamate insecticide given in a dose of 400 mg/kg and of sodium

acetylsalicylate administered in a dose of 400 mg/kg (Shtenberg and Torchinskii, 1977).

The chlorination of water containing various organochlorine pesticides, including HCH, decreases the subsequent LD_{50} levels in mice and rats presumably by conversion of these compounds to more toxic products. This effect was determined by changes in blood erythrocytes, enzymes, and -SH levels, disruption of protein synthesis by the liver, and a decreased rate of weight gain (Shtannikov, et al. 1977).

γ-HCH has also shown to be synergistic or antagonistic with other substances. For example, the sensitivity of mice to pentylenetetrazol at concentrations of 1, 3, 4, 6, and 12 mg/kg body weight was increased by pretreatment of γ-HCH at 10, 7.5, 5.0, 2.5, and 1.2 mg/kg body weight. Specifically, the results showed a significantly higher frequency of convulsions than expected from pentylenetetrazol alone; the convulsive dose threshold was lowered by small, single oral doses of γ-HCH (Hulth, et al. 1976). γ-HCH administered in sublethal doses to rabbits resulted in the suppression of antibody formation in response to Salmonella typhi injections (Desi, 1976).

The toxic effects of γ-HCH have also been antagonized by various tranquilizers (Ulmann, 1972).

Teratogenicity

A study regarding the potential teratogenic effects of γ-HCH involved the p.o. administration in a vegetable oil solution to 4 groups of rats. Groups 1 through 3 were fed 25 mg γ-HCH/kg body weight/day while Group 4 was fed 12 mg γ-HCH/kg body weight/day.

Group numbers 1 and 4 received γ-HCH throughout pregnancy (days 1 to 20), while Group 2 received it throughout placentation and organogenesis (days 7 to 15) and Group 3 during preimplantation period (days 1 to 7). All animals were sacrificed on day 20 and examined. No teratogenic effects were noticed in any of the experimental groups. Females in Group 1 did show, however, increased postimplantation death of embryos: 25.6 percent compared with 11.2 percent in Group 2, 7.6 percent in Group 3, and 9.5 percent in Group 4, and 13.2 percent in nontreated controls (Mametkuliev, 1978). Similar results were obtained by Palmer, et al. (1978) with white rabbits. The effects of lindane on reproductive capacity were also examined by Petrescu, et al. (1974). Four generations of rats (327 animals total) were studied. The investigators reported that 5, 10, or 15 mg/kg body weight administered in the diet resulted in an increase in the average duration of pregnancy from 21 to 22 days in the control animals to 21 to 24 days in the lindane-fed animals. Also, the dosage 15 mg/kg decreased the number of births compared to the number of animals in the parental generation. Numbers fell from 100 births per control parental population to 60 births in lindane-fed animals per parental population. Also noted were delayed opening of the vagina, delayed initiation of first estrous in offspring of experimental groups, and longer estrous cycles in F_2 and F_3 generations. These results are indicative of altered sexual maturation and function and suggest that exposure to lindane during pregnancy causes reduced reproductive capacity in parents and subsequent generations. An increase in the proportion of

stillbirths with succeeding generations of lindane-fed animals was also noted in this study:

Generation	Number of Stillbirths	
	Control	5, 10, 15 mg/kg
F_1	0/50	1/104
F_2	1/45	25/64
F_3	0/56	3/6

In addition, F_1 and F_2 animals of the lindane-fed group exhibited spastic paraplegia, 17/119 and 7/52, respectively.

Mutagenicity

Male mice were administered single intraperitoneal doses of 12.5, 25, and 50 mg δ-HCH/kg (1/8, 1/4, and 1/2 of the LD_{50}) and later mated with females during a seven day period. No mutations or reproductive effects were noted (U.S. EPA, 1973). Mutagenic rates too low to be considered positive were found in host-mediated testing (Buselmair, et al. 1973). However, both the dominant lethal assay and the host mediated assay have been shown to be less sensitive in detecting chemical mutagens than the standard bacterial plate incorporation assay. Many compounds demonstrating no mutagenic activity in the first two assay systems are positive in the latter (Hollstein and McCann, 1979; Poirier and deSerres, 1979). In addition, some alterations in mitotic activity and the karyotype of human lymphocytes cultivated *in vitro* with δ-HCH at concentrations between 0.1 and 10.0 mg/ml have been reported by Tsoneva-Maneva, et al. (1971).

Carcinogenicity

Experimentation with δ-HCH in the early 1950s yielded little or no data in support of carcinogenic activity. Accumulation of epidemiological data (Hans, 1976), however, initiated more recent

investigations into the potential carcinogenic action of HCH. This shift was also prompted by an increase in agricultural use of HCH in Japan. One case report of a Japanese sanitation employee revealed acute leukemia which apparently was associated with occupational exposure to the insecticides HCH and DDT (Hoshizaki, et al. 1970).

When γ-HCH was administered to rats at 800 mg/kg or more in the diet the tumor incidence was not greater than in controls, although average lifespans were reduced (Fitzhugh, et al. 1950). It is important to note, however, that all organs were not microscopically examined. Truhant (1954) supported these findings by feeding diets containing γ-HCH at 25, 50, or 100 mg/kg to rats for two years. Again, no significant increase in tumors was observed.

Nagasaki (1972a) reported the development of liver tumors in all male mice which were fed t-HCH at 660 mg/kg in the diet for 24 weeks. Doses of 66.0 and 6.6 mg/kg/diet did not induce tumors but did increase liver weights. The 66.0 mg/kg dietary level also revealed some cellular hyperplasia. Excessive amounts of α- and β-HCH accumulated in the liver at the 660 mg/kg level. γ- and δ-HCH were found only in trace amounts.

A later experiment involved feeding the α-, β-, γ-, and δ-isomers separately at levels of 100, 250, and 500 mg/kg in the diet. After 24 weeks the experiment was terminated and multiple liver tumors as large as 2.0 centimeters in diameter were observed in all animals given α-HCH at the 500 mg/kg level. The 250 mg/kg α-HCH level resulted in smaller nodules, while no lesions were found in mice fed 100 mg/kg. The various dosages did not produce

any tumors with respect to the other isomers (Nagasaki, et al. 1972b). Pathomorphological investigations by Didenko, et al. (1973) established that the γ-isomer did not induce tumors in mice given intragastric administration at doses of 25 mg/kg twice a week for five weeks.

Hanada, et al. (1973) fed six-week-old mice a basal diet containing 100, 300, and 600 mg/kg of t-HCH or the α-, β-, or γ-isomers for a period of 32 weeks followed by 6 weeks of chemical free diet. At this time, animals were killed and liver tumors were found in 44 percent of the males and 44 percent of the females fed t-HCH. Multiple nodules were found in the liver, although peritoneal invasions or distinct metastases were not found. Liver tumors were found in 68 and 42 percent respectively of the males and females fed the α-isomer. In males and females fed the δ-isomer, liver tumors were found in 13 and 6 percent of the animals, respectively. No tumors were observed in amimals fed either the control or β-HCH diets.

Goto, et al. (1972) reported on feeding eight groups of five-week-old male mice of the ICR-JCL strain diets containing 600 mg/kg of the following compounds: Group 1, t-HCH; Group 2, α-HCH; Group 3, β-HCH; Group 4, γ-HCH; Group 5, a mixture of δ-HCH and ϵ-HCH; Group 6, 1,2,4-trichlorobenzene; Group 7, 2,3,5-trichlorophenol; Group 8, 2,4,5-trichlorophenol. A 9th group received δ-HCH at 300 mg/kg in the diet. After 26 weeks, no increase in weight of the heart, liver, and kidneys was noticed for Groups 6 to 9; however, a marked increase in liver weight was noticed in mice of Groups 1 to 5. Macroscopic examination of the livers revealed

tumors in all mice of Groups 1 and 2; eight of ten mice in Group 5; and five of ten mice in Group 4.

The results of these experiments support the observations that t-HCH and α-HCH frequently cause malignant liver tumors in mice subjected to oral administration of high doses (600 mg/kg) for six months. The same experimental conditions involving β-HCH or γ-HCH produced benign tumors. Malignant tumors were also produced in mice of Group 5, although it was not established whether δ-, ϵ-, or the mixture was responsible for the hepatomas.

The combination of β-, γ-, or δ-HCH with the highly carcinogenic α-HCH revealed no synergistic or antagonistic effect on the production of tumors by α-HCH for dd strains of mice (Ito, et al. 1973). Proliferation of cytoplasmic endoplasmic reticulum as well as nuclear and mitochondrial changes were noticed in the region of hepatocellular carcinomas.

The feeding of α-HCH at 500 mg/kg in the diet to mice for a 24-week period resulted in nodular hyperplasias of the liver (Sugihara, et al. 1975). At the end of initial administration, the ultrastructure of the nodular cells was characterized by large, oval shaped nuclei with clear nucleoplasm. Four weeks after discontinuation, active phagocytotic processes appeared between nodular cells. Although the number of nodular cells decreased after cessation of poisoning, the ones remaining after 12 weeks showed tumorous growth; after 24 weeks, hepatocarcinomas developed. Apparently, the remaining nodular cells are responsible for the development of the hepatocellular carcinomas (Sugihara, et al. 1975).

Some contradiction appears in the literature with respect to the carcinogenic action of the γ-HCH isomer. Thorpe and Walker (1973) noticed tumorigenic action caused by the γ-isomer in the CF_1 strain mice. However, the dose of γ-HCH administered (400 mg/kg in the diet in this experiment) may have been higher than the maximum tolerated dose. Associated liver enlargement and hepatomas may have also resulted from nonspecific toxic effects. Three percent of the females and 17 percent of the males fed γ-HCH survived the duration of the experiment.

The National Cancer Institute (NCI) conducted a bioassay for the possible carcinogenicity of γ-HCH to Osborne-Mendel rats and $B6C3F_1$ mice. Administration continued for 80 weeks at 2 dose levels: time-weighted average dose for male rats was 236 and 472 mg/kg in the diet; for female rats, 135 and 270 mg/kg; and for all mice, 80 and 160 mg/kg. No statistically significant incidence of tumor occurrence was noted in any of the experimental rats as compared to the controls. At the lower dose concentration in male mice, the incidence of hepatocellular carcinoma was significant when compared to the controls, but not significant in the higher dose males. "Thus, the incidence of hepatocellular carcinoma in male mice cannot clearly be related to treatment." The incidence of hepatocellular carcinoma among female mice was not significant. Consequently, the carcinogenic activity of γ-HCH in mice is questionable (NCI, 1977).

Experiments by Nagasaki, et al. (1972a,b) with other strains produced negative results. According to Miura, et al. (1974), the toxicity of t-HCH and HCH isomers varies significantly among

different strains of mice, with the CF_1 strain being particularly susceptible. Feeding 500 mice of the Chbi:NMRI(SPF) strain γ-HCH at levels of 12.5, 25, and 50 mg/kg in the food for 80 weeks revealed no compound-induced lymphatic leukemia, no malignant hemangioendotheliomas, and no liver cell adenomas (Herbst, et al. 1975). Electron-microscopical examinations of SPF mice which were fed the same concentrations, provided no evidence of γ-HCH-induced fine structural hepatocellular alterations (Weisse and Herbst, 1977).

In a study by Ito, et al. (1975) male Wistar-derived rats were fed several isomers of HCH in the diet for 72 weeks. The α-HCH isomer was administered at 500, 1,000, and 1,500 mg/kg of diet, β-HCH at 500 and 1,000 mg/kg, γ-HCH at 500 mg/kg and δ-HCH at 500 and 1,000 mg/kg. The 500 mg/kg level of all isomers produced no neoplastic changes, cell infiltration, fatty changes, fibrosis, or bile duct proliferation, but liver weights did increase in all groups except the δ-HCH-treated rats. Only the α-HCH-treated group revealed tumor development. No metastases were seen and no tumorous growths developed in any of the other dietary groups (Ito, et al. 1975).

One instance of carcinogenic synergism of γ-HCH in combination with leupeptin showed a 5-fold increase in hepatic nodular hyperplasia (Arai, et al. 1978). Other experiments have shown γ-HCH to have an antagonistic effect on the hepatocellular carcinoma induction by aflatoxin B1 in male albino rats (Angsubhakorn, et al. 1978).

No pertinent data are currently available in the scientific literature on the carcinogenicity of the δ- and the ϵ-isomers of

HCH. Furthermore, the δ- and ϵ-isomers are rarely detected in the environment.

CRITERION FORMULATION

Existing Guidelines and Standards

The FAO/WHO ADI is 1 µg/kg/day and was revised downward to that figure from 12.5 mg/kg/day originally set by FAO/WHO in 1972 (NAS, 1977). Barney (1969) showed the average daily intake of HCH for U.S. citizens to be 0.002 µg/kg/day from the air and 0.07 µg/kg/day from foodstuffs, clearly below the established level of 1 µg/kg/day.

The EPA set the tolerance for animal fats at 7 ppm, and 0.3 ppm for milk. One ppm is the tolerance level for most fruits and vegetables. Finished drinking water should contain no more than 0.004 ppm. The maximum air concentration that is allowed by the EPA is 0.5 mg/m^3 of air. Cases of HCH poisoning in Japan have shown concentrations of 23 and 59 mg/m^3 at factories involved in the manufacture of HCH. In both cases a number of workers became ill with convulsions. It is clear that research is needed concerning the effects of long-term, low-level air concentrations of the HCH isomers.

Current Levels of Exposure

Considering the steady decline in the use of organochlorine insecticides, it is likely that HCH concentrations will continue to fall. This should also lower the amount of human exposure of HCH by oral ingestion. Dermal and inhalation, however, are recognized sources of contamination for those involved in the manufacture, use, and formulation of HCH and its isomers.

There is considerable pressure in the European countries to ban all organochlorine insecticides except lindane (δ -HCH). It is

strongly believed by many that γ-HCH does not represent a pollution problem. It is recognized by the same scientists that α- and β-HCH do represent a significant hygienic problem. α- and β-HCH are accumulated up the food chain, e.g., Japanese rice $\longrightarrow$ rice straw $\longrightarrow$ cattle $\longrightarrow$ cattle products $\longrightarrow$ man. Technical grade HCH (t-HCH) contains a significant amount of the α- and β-isomers, so production of t-HCH should be restricted and only production of γ-HCH allowed. The presence of the α- and β-isomers has in part given rise to the hypothesis that the γ-isomer can be transformed to the unwanted isomers. Experimental isomerization has occurred (Newland, et al. 1969), but only under anaerobic aquatic conditions and probably by microorganisms. There is a lack of bioisomerization in mammals. It should not be overlooked that α-HCH, despite its relatively short half-life, will be detected for a long time following the use of t-HCH, in which it is present in high proportion (60 to 70 percent). Practical proof of this theory is shown by the fact that in countries where the use of t-HCH was terminated (and no γ-HCH had been used), residues of α- and β-HCH were found for many years. It is known that in such cases, the relative share of β-HCH of the total HCH residues is increasing. If γ-HCH is used exclusively in an area, then the share of γ-HCH of the total HCH residues will vary in accordance with the extent of application, and the other isomers will show a downward trend.

Special Groups at Risk

t-HCH or γ-HCH is not currently manufactured in the U.S. Use of t-HCH has been banned, but γ-HCH is still approved for use. All

γ-HCH used in the U.S. is currently imported; there is no exposure during manufacture in this country. Formulators, distributors and users of the product certainly represent a special risk group. The major use of γ-HCH in recent years has been to pretreat seeds (42 percent in 1974), representing a source of exposure for employees of the seed companies. Agricultural workers could be exposed during handling and planting of the seed and during application to crops.

Basis and Derivation of Criteria

The animal carcinogenicity data from Ito, et al. (1976), Goto, et al. (1972), Thorpe and Walker, (1973), and Nagasaki, et al. (1972a) have been used to develop water quality criteria for α-, β-, γ-, and technical-HCH, respectively. These criteria have been developed by the Carcinogen Assessment Group of EPA. The assessment is given in Appendix I.

Under the Consent Decree in NRDC v. Train, criteria are to state "recommended maximum permissible concentrations (including where appropriate, zero) consistent with the protection of aquatic organisms, human health, and recreational activities." α-HCH, β-HCH, γ-HCH and t-HCH are suspected of being human carcinogens. Because there is no recognized safe concentration for a human carcinogen, the recommended concentration of α-HCH, β-HCH, γ-HCH, and t-HCH in water for maximum protection of human health is zero.

Because attaining a zero concentration level may be infeasible in some cases and in order to assist the Agency and States in the possible future development of water quality regulations, the concentrations of α-HCH, β-HCH, γ-HCH, and t-HCH corresponding to

several incremental lifetime cancer risk levels have been estimated. A cancer risk level provides an estimate of the additional incidence of cancer that may be expected in an exposed population. A risk of 10^{-5} for example, indicates a probability of one additional case of cancer for every 100,000 people exposed, a risk of 10^{-6} indicates one additional case of cancer for every million people exposed, and so forth.

In the Federal Register notice of availability of draft ambient water quality criteria, EPA stated that it is considering setting criteria at an interim target risk level of 10^{-5}, 10^{-6}, or 10^{-7} as shown in the tables following.

α-HCH

Exposure Assumptions (per day)	Risk Levels and Corresponding Criteria (1)			
	0	10^{-7}	10^{-6}	10^{-5}
2 liters of drinking water and consumption of 6.5 g fish and shellfish.(2)	0	0.92 ng/l	9.2 ng/l	92 ng/l
Consumption of fish and shellfish only.	0	3.10 ng/l	31.0 ng/l	310 ng/l

β-HCH

Exposure Assumptions (per day)	Risk Levels and Corresponding Criteria (1)			
	0	10^{-7}	10^{-6}	10^{-5}
2 liters of drinking water and consumption of 6.5 g fish and shellfish.(2)	0	1.63 ng/l	16.3 ng/l	163 ng/l
Consumption of fish and shellfish only.	0	5.47 ng/l	54.7 ng/l	547 ng/l

γ-HCH

Exposure Assumptions (per day)	Risk Levels and Corresponding Criteria(1)			
	0	10^{-7}	10^{-6}	10^{-5}
2 liters of drinking water and consumption of 6.5 g fish and shellfish.(2)	0	1.86 ng/l	18.6 ng/l	186 ng/l
Consumption of fish and shellfish only.	0	6.25 ng/l	62.5 ng/l	625 ng/l

t-HCH

Exposure Assumptions (per day)	Risk Levels and Corresponding Criteria(1)			
	0	10^{-7}	10^{-6}	10^{-5}
2 liters of drinking water and consumption of 6.5 g fish and shellfish.(2)	0	1.23 ng/l	12.3 ng/l	123 ng/l
Consumption of fish and shellfish only.	0	4.14 ng/l	41.4 ng/l	414 ng/l

(1) Calculated by applying a linearized multistage model as discussed in the Human Health Methodology Appendices to the October 1980 Federal Register notice which announced the availability of this document. Appropriate bioassay data used in the calculation of the model are presented in Appendix I. Since the extrapolation model is linear at low doses, the additional lifetime risk is directly proportional to the water concentration. Therefore, water concentrations corresponding to other risk levels can be derived by multiplying or dividing one of the risk levels and corresponding water concentrations shown in the table by factors such as 10, 100, 1,000, and so forth.

(2) Approximately 30 percent of the α-HCH, β-HCH, γ-HCH, and t-HCH exposure results from the consumption of aquatic organisms which exhibit an average bioconcentration potential of 130-fold. The remaining 70 percent of α-HCH, β-HCH, γ-HCH, and t-HCH exposure results from drinking water.

Concentration levels were derived assuming a lifetime exposure to various amounts of HCH (1) occurring from the consumption of both drinking water and aquatic life grown in waters containing the corresponding HCH concentrations and, (2) occurring solely from consumption of aquatic life grown in the waters containing the corresponding HCH concentrations. Although total exposure information for HCH is discussed and an estimate of the contributions from other sources of exposure can be made, these data will not be factored into ambient water quality criteria formulation until additional analyses can be made. The criteria presented, therefore, assume an incremental risk from ambient water exposure only.

Water quality criteria for the δ- and ϵ-isomers of HCH have not been established because of insufficient data. These isomers have not been detected in the environment and would not appear to be a health risk. The water quality criteria for hexachlorocyclohexane are summarized as follows:

Form	Criteria
α-isomer	92 ng/l*
β-isomer	163 ng/l*
γ-isomer	186 ng/l*
δ-isomer	none
ϵ-isomer	none
technical	123 ng/l

*At a risk level of one in 100,000.

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APPENDIX I

Summary and Conclusions Regarding the Carcinogenicity of Hexachlorocyclohexane

Hexachlorocyclohexane (HCH;BHC) is a saturated chlorinated hydrocarbon which has insecticidal properties. Technical grade HCH is composed of five basic isomers including the alpha (α), beta (β), gamma (γ), delta (δ), and epsilon (ϵ) isomers. The gamma isomer (gamma-HCH; γ-BHC; Lindane) has the lowest melting point (112°C) and also has the highest acute toxicity of these five isomers of HCH.

So far, 2,4,6-trichlorophenol is the only metabolite of gamma-HCH shown to be an animal carcinogen (National Cancer Institute, 1979).

Reports concerning the mutagenicity of hexachlorocyclohexane relate to the gamma isomer. Although gamma-HCH was found to be mutagenic in microbial tests using Salmonella typhimurium TA 1535 and TA 1538 with metabolic activation (Ames test), the host-mediated assay, and the dominant lethal test in rats, other reports indicate that it does not have significant mutagenic activity.

Numerous reports concerning the carcinogenicity of technical hexachlorocyclohexane and its isomers are in the literature. An increased incidence of liver tumors was reported in male and/or female mice of various strains fed technical HCH (Goto, et al. 1972; Hanada, et al. 1973; Nagasaki, et al. 1972a), alpha-HCH (Goto, et al. 1972; Hanada, et al. 1973; Ito, et al. 1973, 1976; Nagasaki, et al. 1972b), beta-HCH (Goto, et al. 1972; Thorpe and

Walker, 1973) and gamma-HCH (Goto, et al. 1972; Hanada, et al. 1973; National Cancer Institute, 1977; Thorpe and Walker, 1973). Male rats fed alpha-HCH for up to 72 weeks also developed liver tumors (Ito, et al. 1975). One report in the literature (Goto, et al. 1972) detailed an increase of liver tumors in mice fed a mixture of delta and epsilon isomers of HCH, but there were no studies which used individual delta or epsilon isomers.

The induction of liver tumors in male and female mice from the administration of either technical HCH, alpha-HCH, beta-HCH, or gamma-HCH and the induction of liver tumors in male rats from the administration of alpha-HCH indicates that technical, alpha-, beta-, and gamma-HCH are likely to be human carcinogens.

The water quality criterion for technical HCH is based on the induction of liver tumors in male dd mice fed 660 ppm technical hexachlorocyclohexane for 24 weeks (Nagasaki, et al. 1972a). It is concluded that the water concentration of technical HCH should be less than 123 ng/l in order to keep the lifetime cancer risk below 10^{-5}.

The water quality criterion for alpha-HCH is based on the induction of liver tumors in male DDY mice fed 500 ppm alpha-hexachlorocyclohexane for 24 weeks (Ito, et al. 1975). It is concluded that the water concentration of alpha-HCH should be less than 92 ng/l to keep the lifetime risk below 10^{-5}.

The water quality criterion for beta-HCH is based on the induction of liver tumors in male ICR-JCL mice fed 600 ppm beta-hexachlorocyclohexane for 26 weeks (Goto, et al. 1972). It is

concluded that the water concentration of beta-HCH should be less than 163 ng/l in order to keep the lifetime risk below 10^{-5}.

The water quality criterion for gamma-HCH is based on the induction of liver tumors in male CF_1 mice fed 400 ppm gamma-hexachlorocyclohexane for 110 weeks (Thorpe and Walker, 1973). It is concluded that a water concentration of gamma-HCH should be less than 186 ng/l in order to keep the lifetime cancer risk below 10^{-5}.

Because of insufficient data, a water quality criterion cannot be established for either the delta or epsilon isomer of hexachlorocyclohexane.

Summary of Pertinent Data

The water quality criterion of alpha-hexachlorochyclohexane is derived from the oncogenic effects observed in the liver of male DDY mice fed 500 ppm alpha-HCH in the diet (Ito, et al. 1975). The time-weighted average dose of 65 mg/kg/day was given in the feed for 24 weeks. The criterion is calculated from the following parameters:

Dose (mg/kg/day)	Incidence (no. responding/no. tested)
0	0/18
65	20/20

le = 24 weeks
Le = 90 weeks
L = 90 weeks
w = 0.0357 kg
R = 130 l/kg

With these parameters the carcinogenic potency factor for humans, q_1^*, is 2.67 $(mg/kg/day)^{-1}$. The resulting water concentration of alpha-hexachlorocyclohexane calculated to keep the individual lifetime cancer risk below 10^{-5} is 92 ng/l.

Summary of Pertinent Data

The water quality criterion for beta-hexachlorocyclohexane is derived from the oncogenic effects observed in the liver of male ICR-JCL mice fed 600 ppm beta-HCH in the diet (Goto, et al. 1972). The time-weighted average dose of 78 mg/kg/day was given in the feed for 26 weeks. The criterion is calculated from the following parameters:

Dose (mg/kg/day)	Incidence (no. responding/no. tested)
0	0/10
78	10/10

le = 182 days w = 0.0475 kg

Le = 630 days R = 130 l/kg

L = 630 days

With these parameters the carcinogenic potency factor for humans, q_1^*, is 1.514 $(mg/kg/day)^{-1}$. The resulting water concentration of beta-hexachlorocyclohexane calculated to keep the individual lifetime cancer risk below 10^{-5} is 163 ng/l.

Summary of Pertinent Data

The water quality criterion for gamma-hexachlorocyclohexane is derived from the oncogenic effects observed in the liver of male CF_1 mice fed 400 ppm gamma-HCH in the diet (Thorpe and Walker, 1973). The time-weighted average dose of 52 mg/kg/day was given in the feed for 110 weeks. The criterion is calculated from the following parameters:

Dose (mg/kg/day)	Incidence (no. responding/no. tested)
0	11/45
52	27/28

le = 770 days w = 0.030 kg

Le = 770 days R = 130 l/kg

L = 770 days

With these parameters the carcinogenic potency factor for humans, q_1^*, is 1.326 $(mg/kg/day)^{-1}$. The resulting concentration of gamma-hexachlorocyclohexane calculated to keep the individual lifetime cancer risk below 10^{-5} is 186 ng/l.

Summary of Pertinent Data

The water quality criterion for technical hexachlorocyclohexane is derived from the oncogenic effects observed in the liver of male dd mice fed 660 ppm technical HCH in the diet (Nagasaki, et al. 1972a). The time-weighted average dose of 85.8 mg/kg/day was given in the feed for 24 weeks. The criterion is calculated from the following parameters:

Dose (mg/kg/day)	Incidence (no. responding/no. tested)
0	0/14
85.8	20/20

le = 24 weeks
Le = 90 weeks
L = 90 weeks
w = 0.0364 kg
R = 130 l/kg

With these parameters the carcinogenic potency factor for humans, q_1^*, is 2.0 $(mg/kg/day)^{-1}$. The resulting water concentration of technical hexachlorocyclohexane calculated to keep the individual lifetime cancer risk below 10^{-5} is 123 ng/l.